(19) DANMARK

(10) DK/EP 1907382 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 413/04 (2006.01)* *A 61 K 31/421 (2006.01)* *A 61 K 31/4425 (2006.01)* *A 61 K 31/4439 (2006.01)* *A 61 K 31/506 (2006.01)* *A 61 P 25/00 (2006.01)* *C 07 D 213/89 (2006.01)* *C 07 D 271/06 (2006.01)* *C 07 D 271/10 (2006.01)* *C 07 D 401/04 (2006.01)* *C 07 D 407/04 (2006.01)* *C 07 D 413/06 (2006.01)* *C 07 D 413/14 (2006.01)* *C 07 D 417/14 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2015-08-31**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2015-05-27**

(86) Europæisk ansøgning nr.: **06769520.5**

(86) Europæisk indleveringsdag: **2006-07-26**

(87) Den europæiske ansøgnings publiceringsdag: **2008-04-09**

(86) International ansøgning nr.: **PT2006000020**

(87) Internationalt publikationsnr.: **WO2007013830**

(30) Prioritet: **2005-07-26 GB 0515327** **2006-04-20 EP 06008203** **2006-05-30 EP 06011073**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR**

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(54) Benævnelse: **NITROCATECHOLDERIVATER SOM COMT-INHIBITORER**

(56) Fremdragne publikationer:
EP-A- 1 167 342
TERVO, ANU J. ET AL: "A structure-activity relationship study of catechol-O-methyltransferase inhibitors combining molecular docking and 3D QSAR methods" JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN , VOLUME DATE 2003, 17(12), 797-810 CODEN: JCADEQ; ISSN: 0920-654X, 2004, XP002402314
LEARMONTH, DAVID A. ET AL: "Chemical Synthesis and Characterization of Conjugates of a Novel Catechol-O-methyltransferase Inhibitor" BIOCONJUGATE CHEMISTRY , 13(5), 1112-1118 CODEN: BCCHES; ISSN: 1043-1802, 2002, XP002402315

Fortsættes ...

DESCRIPTION

[0001] This invention relates to novel substituted nitrocatechols, their use in the treatment of some central and peripheral nervous system disorders and pharmaceutical compositions containing them.

[0002] Despite being used in clinical practice for several decades, levodopa (L-DOPA) continues to be the gold standard drug for the symptomatic treatment of Parkinson's disease. This has helped to maintain keen interest in the development of inhibitors of the enzyme catechol-O-methyltransferase (COMT) based on the hypothesis that inhibition of this enzyme may provide clinical improvements in patients afflicted by Parkinson's disease undergoing treatment with L-DOPA and a peripheral amino acid decarboxylase (AADC) inhibitor. The rationale for the use of COMT inhibitors as adjuncts to L-DOPA/AADC therapy is based on their ability to reduce metabolic *O*-methylation of L-DOPA to 3- *O*-methyl-L-DOPA (3-OMD). The duration of L-DOPA induced clinical improvement is brief as a result of the short in vivo half-life of L-DOPA which contrasts with the long half-life of 3-OMD. Additionally, 3-OMD competes with L-DOPA for transport across the blood-brain barrier (BBB), which means that only a very limited amount of an orally administered dose of L-DOPA actually reaches the site of action, i.e. the brain. Commonly, within only a few years of starting L-DOPA therapy with the usual dosage regime, L-DOPA induced clinical improvement declines at the end of each dose cycle, giving rise to the so-called 'wearing-off' pattern of motor fluctuations. A close relationship between the 'wearing-off' phenomenon and accumulation of 3-OMD has been described (Tohgi, H., et al., Neurosci. Letters, 132:19-22, 1992). It has been speculated that this may result from impaired brain penetration of L-DOPA due to competition for the transport system across the BBB with 3-OMD (Reches, A. et al., Neurology, 32:887-888, 1982) or more simply that there is less L-DOPA available to reach the brain (Nutt, J.G., Fellman, J.H., Clin. Neuropharmacol., 7:35-49, 1984). In effect, COMT inhibition protects L-DOPA from metabolic breakdown in the periphery through O-methylation, such that with repeated doses of L-DOPA, the mean plasma L-DOPA concentration is raised. In addition to reduced competition for transport into the brain, a significantly greater percentage of the orally administered dose of L-DOPA is able to reach the site of action. Thus COMT inhibition serves to increase the bioavailability of L-DOPA and the duration of antiparkinsonian action is prolonged with single doses of L-DOPA (Nutt, J.G., Lancet, 351:1221-1222,1998).

[0003] The most potent COMT inhibitors thusfar reported are 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone (Tolcapone, Australian pat. AU-B-69764/87), (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide (Entacapone, German pat. DE 3740383 A1) and BIA 3-202 (American pat. US 6512136) which all have inhibition constants in the low nanomolar range. Although sharing essentially the same pharmacophore, tolcapone differs from entacapone and BIA 3-202 in that it easily enters the central nervous systems (CNS) and is able to inhibit cerebral COMT as well as peripheral COMT. It could be speculated that central inhibition may be less important if the more significant action of inhibiting COMT is to prevent breakdown of L-DOPA in the periphery. Indeed, the use of COMT inhibitors which do not penetrate into the brain at clinically relevant doses may avoid potential undesired CNS side-effects of these agents.

[0004] Another serious issue which has emerged since these COMT inhibitors were introduced into clinical practice relates to the potential of these nitrocatechol-based xenobiotics to cause severe liver damage (hepatotoxicity). Indeed, shortly after its launch, tolcapone was withdrawn from the market after several cases of hepatotoxicity were reported including three unfortunate deaths from fatal fulminant hepatitis. Today tolcapone can only be used in Parkinsonian patients who are unresponsive to other treatments and strictly only with regular monitoring of liver function, which is expensive and inconvenient for the patient. Although the actual mechanistic causes of the liver toxicity associated with tolcapone are not fully understood, in vitro studies have shown that tolcapone may be reduced metabolically to reactive intermediates and it has been speculated that these may form covalent adducts with hepatic proteins resulting in hepatocellular injury (Smith, K.S. et al, Chem. Res. Toxicol., 16:123-128,2003).

[0005] Entacapone on the other hand, although sharing the same nitrocatechol pharmacophore with tolcapone, is not associated with liver toxicity and is generally regarded as a safe drug. Unfortunately however, entacapone is a significantly less potent COMT inhibitor than tolcapone and has a much shorter in-vivo half-life. This means that entacapone has a very limited duration of effect and as a consequence, the drug must be administered in very high doses with every dose of L-DOPA taken by the patient. As such, the clinical efficacy of entacapone has been questioned - indeed a recent study (Parashos, S.A. et al., Clin. Neuropharmacol., 27(3): 119-123, 2004) revealed that the principal reason for discontinuation of entacapone treatment in Parkinson's disease patients was a perceived lack of efficacy.

[0006] EP 1 167 342 A1 discloses carbonyl substituted 3,4-dihydroxy-5-nitrobenzoyl pharmacophore for COMT inhibitors.

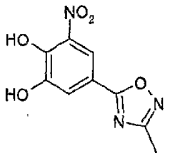
[0007] The article by Terwo et al, Journal of Computer-Aided-Molecular Design, 17(12), 797-810, 2004 , discloses a structure-activity relationship study of COMT inhibitors combining molecular docking and 3D QSAR methods.

[0008] The article by Learmonth et al, Bioconjugate Chemistry, 13(5), 1112-1118, 2002 , discloses the chemical synthesis and characterization of conjugates of COMT inhibitors.

[0009] In summary, there still remains a clear clinical requirement for a safe and effective COMT inhibitor for adjunctive therapy in the management of the symptoms of Parkinson's disease. Preferably, the COMT inhibitor should be endowed with greater potency and duration of COMT inhibition than entacapone, which would lead to greater clinical efficacy. More preferably, the COMT inhibitor should, unlike tolcapone, have limited access to the CNS, i.e. it should preferentially inhibit peripheral COMT rather than central COMT. Even more preferably, the COMT inhibitor should combine the aforementioned features and in addition should not be endowed with potential to cause liver toxicity as seen with tolcapone.

[0010] We have now surprisingly found that certain nitrocatechols are very potent COMT inhibitors which are also devoid of, or have greatly reduced, toxicity risk. Furthermore, it has been unexpectedly ascertained that it is the chemical functionality of the non-catecholic substituent connected to the heterocyclic ring that determines the lack of toxic effects of the compounds.

[0011] To date, there has been only one reported example of a nitrocatecholic [1,2,4]-oxadiazole in the prior art (Example 75 of Australian pat. AU-B-69764/87), this being 5-(3-methyl-1,2,4-oxadiazol-5-yl)-3-nitropyrocatechol 1, which has the chemical structure shown below;

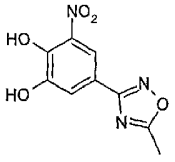


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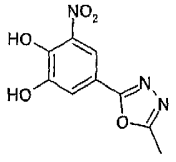
[0012] This substance is a 3,5-disubstituted-[1,2,4]-oxadiazole with the methyl group occupying position C-3 of the heterocyclic oxadiazolyl ring and the nitrocatecholic pharmacophore attached to C-5.

[0013] We have studied the oxadiazolyl compound 1 mentioned above and found it to be moderately active in the COMT inhibition assay (59% of control, see experimental section). Unfortunately however, compound 1 presents a significant toxicity risk (55% cell viability, see experimental section). As such, this particular compound 1 cannot be considered to represent an adequate solution to the present problem of a providing a potent and clinically safe COMT inhibitor.

[0014] We have surprisingly found that if the central ring is substituted with a pyridyl ring in oxidised form (i.e. pyridine N-oxide), that the resulting pyridine N-oxide compounds exhibit greatly reduced toxicity, or are even devoid of toxicity risk, whilst it is still concomittantly possible to maintain COMT inhibition superior to entacapone. If the position of the nitrocatechol pharmacophore is 'switched' from C-5 to the C-3 position of the oxadiazole ring, then the resulting compounds are usually less active in terms of COMT inhibition. The regioisomeric 1,3,4-oxadiazoles, wherein the nitrocatechol pharmacophore is attached to C-2 of the oxadiazolyl central ring are also usually less active in terms of COMT inhibition. For example, consider the regioisomers 2 and 3 of the prior art oxadiazole 1 which we have also synthesised and evaluated in vivo;



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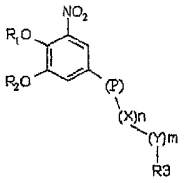


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[0015] Although both 2 and 3 each present a reduced toxicity risk in relation to 1, in terms of COMT inhibition compound 2 displayed only 79% of control and compound 3 was only marginally better at 64%. Thus it can be concluded that it is the combination of the correct positional arrangement of the heteroatoms in the central oxadiazole ring and the incorporation of the pyridine N-oxide functionality is unexpectedly crucial for obtaining synergy between high COMT inhibitory activity and safety for this type of COMT- inhibitor.

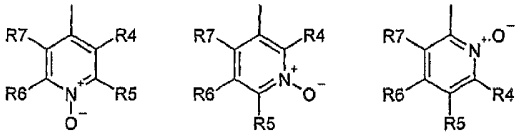
[0016] Accordingly, the present invention relates to nitrocatecholic COMT inhibitors which are devoid of, or have greatly reduced, toxicity risk. Furthermore, it has been unexpectedly ascertained that it is the introduction of a nitrogen-based heterocyclic group in N-oxidised form, such as, for example, a pyridine N-oxide, that determines the lack of toxic effects of the

nitrocatecholic compounds. We have further surprisingly found that compounds of general formula I are COMT inhibitors which are endowed with balanced properties of bioactivity, bioavailability and, in particular, safety:



(I)

wherein R_1 and R_2 are independently from each other hydrogen; Y represents an atom of oxygen or sulphur; n represents the number 0, 1, 2 or 3 and m represents the number 0 or 1; R_3 represents a pyridine N-oxide group according to the formula A, B or C, which is connected as indicated by the unmarked bond:



A B C

where R_4, R_5, R_6 and R_7 independently from each other represent hydrogen, C_1-C_6-alkyl, C_1-C_6-thioalkyl, C_1-C_6-alkoxy, C_6-C_{12}-aryloxy or a C_6-C_{12}-thioaryl group, C_1-C_6-alkanoyl or C_7-C_{13}-aroyl group, amino, C_1-C_6- alkylamino, C_1-C_6-dialkylamino, C_3-C_{12}-cycloalkylamino, C_3-C_{12}-heterocycloalkylamino, C_1-C_6-alkylsulphonyl, C_6-C_{12}-arylsulphonyl, halogen, C_1-C_6-haloalkyl, trifluoromethyl, cyano, nitro or a heteroaryl group; or two or more of residues R_4, R_5, R_6 and R_7 taken together represent aliphatic or heteroaliphatic rings or aromatic or heteroaromatic rings and wherein P represents a central unit, which is selected from the regioisomers of 1,3,4-oxadiazol-2,5-diyl and 1,2,4-oxadiazol-3,5-diyl.

[0017] In the above definition, the regioisomers of the central unit include both regioisomers realizable by exchange of the nitrocatechol moiety and the $-(X)_n-(Y)_m-R_3$ moiety.

[0018] Preferably, C_1-C_6-alkyl residues represent methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl or hexyl. Preferably, C_1-C_6-thioalkyl residues represent thiomethyl, thioethyl, thio-n-propyl, thio-isopropyl, thio-n-butyl, thio-n-pentyl and thio-n-hexyl. Preferably, C_1-C_6-alkoxy residues represent methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy and tert-butoxy. Preferably, C_6-C_{12}-aryloxy residues represent phenoxy or naphthoxy which may optionally be substituted. Preferably, C_6-C_{12}-thioaryl residues represent thiophenyl and thionaphthyl which may optionally be substituted. Preferably, C_1-C_6-alkanoyl residues represent methanoyl, ethanoyl, propanoyl or butanoyl. Preferably, C_7-C_{13}-aroyl residues represent benzoyl and naphthoyl. Preferably, C_1-C_6-alkylamino residues represent methylamino, ethylamino, n-propylamino, isopropylamino and n-butylamino. Preferably, C_1-C_6-dialkylamino residues represent dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, di-isopropylamino, methylethylamino, methylpropylamino and ethylpropylamino. Preferably, C_3-C_{12}-cycloalkylamino residues represent pyrrolidino, piperidino, cyclohexylamino and dicyclohexylamino. Preferably, C_3-C_{12}-heterocycloalkylamino residues represent morpholino, 2,6-dimethylmorpholino, 3,5-dimethylmorpholino, piperazino, N-methylpiperazino and N-ethylpiperazino. Preferably, C_1-C_6-alkylsulphonyl or C_6-C_{12}-arylsulphonyl residues represent methylsufonyl, ethylsulfonyl, phenylsulfonyl, and tolylsulfonyl. Preferably, halogen residues represent chloro, bromo, iodo and fluoro. Preferably, C_1-C_6-haloalkyl represents chloromethyl, fluoromethyl, dichloromethyl, difluoromethyl, trichloromethyl and trifluoromethyl. Preferably, heteroaryl residues represent pyridyl, pyrimidyl, isoxazolyl, oxazolyl, isoxadiazolyl, oxadiazolyl, triazolyl and tetrazolyl. In cases where two or more of residues R_4, R_5, R_6 and R_7 taken together represent aliphatic or heteroaliphatic rings or aromatic or heteroaromatic rings, preferred combined residues are indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, naphthyridinyl, isoquinolyl and quinolyl.

[0019] Described are compounds wherein the central unit may be selected from a heteroaromatic five-membered ring which includes 1 to 4 of the heteroatoms N, O and S. The central unit P may be selected from the regioisomers of 1,3,4-oxadiazol-2,5-diyl, 1,2,4-oxadiazol-3,5-diyl, 4-methyl-4H-1,2,4-triazol-3,5-diyl, 1,3,5-triazin-2,4-diyl, 1,2,4-triazin-3,5-diyl, 2H-tetrazol-2,5-diyl, 1,2,3-thiadiazol-4,5-diyl, 1-alkyl-3-(alkoxycarbonyl)-1 H-pyrrol-2,5-diyl, wherein alkyl is represented by methyl, ethyl, n-propyl and n-butyl and wherein alkoxy is represented by methoxy, ethoxy, n-propoxy and isopropoxy, 1-alkyl-1-H-pyrrol-2,5-diyl, wherein alkyl is represented by methyl, ethyl, n-propyl and n-butyl, thiazol-2,4-diyl, 1-H-pyrazol-1,5-diyl, oxazol-2,4-diyl, carbonyl, 1H-imidazol-1,5-diyl, isoxazol-3,5-diyl, furan-2,4-diyl, 3-alkoxycarbonylfuran-2,4-diyl, wherein alkoxy is represented by methoxy, ethoxy, n-propoxy and isopropoxy. In the present invention, the central unit P is selected from 1,3,4-oxadiazol-2,5-diyl and 1,2,4- oxadiazol-3,5-diyl.

[0020] Preferred compounds of the above general formula (I) having a 1,2,4-oxadiazol-3,5-diyl as central unit include 5-[3-(3,5-dichloro-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-chloro-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1 ,2-diol, 5-[3-(2-morpholin-4-yl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 3-nitro-5-[3-(1-oxy-4-trifluoromethyl-pyridin-3-yl)-1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, 5-[3-(4-bromo-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-chloro-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-morpholin-4-yl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 3-nitro-5-[3-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, 5-[3-(2-methyl-1-oxy-6-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(6-methyl-1-oxy-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2,6-dimethyl-1-oxy-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-methyl-1-oxy-6-phenyl-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(6-methyl-1-oxy-2-phenyl-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-bromo-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-chloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-bromo-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, 5-[3-(2-bromo-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, 5-[3-(2-chloro-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, 5-[3-(2,5-dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, 5-[3-(2-bromo-5-chloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, and 3-nitro-5-[3-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-fluoropyridine 1-oxide, 4-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-2-fluoropyridine 1-oxide, 2-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-5-yl)-4,6-dimethylpyridine 1-oxide.

[0021] Preferred compounds of the above general formula (I) having a 1,3,4-oxadiazol-2,5-diyl as central unit include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide,3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1 -oxide, 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-fluoropyridine 1-oxide, 4-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-fluoropyridine 1-oxide, 2-(5-(3 ,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)-4,6-dimethylpyridine 1-oxide.

[0022] Described are compounds of the above general formula (I) having a 4-methyl-4H-1,2,4-triazol-3,5-diyl as central unit include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-

(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-fluoropyridine 1-oxide, 4-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-2-fluoropyridine 1-oxide, 2-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-6-methylpyridine 1-oxide and 2-bromo-5-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4,6-dimethylpyridine 1-oxide.

[0023] Described are compounds of the above general formula (I) having a 1,3,5-triazin-2,4-diyl as central unit include 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, and 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-5-(trifluoromethyl)pyridine 1-oxide.

[0024] Described are compounds of the above general formula (I) having a 1,2,4-triazin-3,5-diyl as a central unit include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-4-(trifluorormethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-5-(trifluoromethyl)pyridine 1-oxide, 4-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-fluoropyridine 1-oxide and 2-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-6-fluoropyridine 1-oxide.

[0025] Described are compounds of the above general formula (I) having a (Z)-1-cyanoethen-1,2-diyl moiety as central unit include (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4-(trifluorornethyl)pyridine 1-oxide, (Z)-2-chloro-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4,6-dimethylpyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, (Z)-5-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-(trifiuoromethyl)pyridine 1-oxide, (Z)-5-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, (Z)-3,5-dichloro-4-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)pyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, (Z)-2-bromo-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4,5,6-trimethylpyridine 1-oxide, (Z)-2-chloro-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4,5,6-trimethylpyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-(trifluoromethyl)pyridine 1-oxide, (Z)-2,5-dichloro-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4,6-dimethylpyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-5-(trifluoromethyl)pyridine 1-oxide, (Z)-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-fluoropyridine 1-oxide, (Z)-4-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-2-fluoropyridine 1-oxide, (Z)-2-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-6-fluoropyridine 1-oxide, (Z)-2-chloro-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-6-methylpyridine 1-oxide, (Z)-2-bromo-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-6-methylpyridine 1-oxide, and (Z)-2-bromo-5-chloro-3-(1-cyano-2-(3,4-dihydroxy-5-nitrophenyl)vinyl)-4,6-dimethylpyridine 1-oxide.

[0026] Described are compounds of the above general formula (I) having as central unit a furan-2,4-diyl or a 3-alkoxycarbonylfuran-2,4-diyl moiety, wherein alkoxy is represented by methoxy, ethoxy, n-propoxy and isopropoxy, include 3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-methyl-6-(trifiuorornethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)furan-2-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-fluoropyridine 1-oxide, 4-(4-

(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-fluoropyridine 1-oxide, 2-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-4,6-dimethylpyridine 1-oxide.

[0027] Described are compounds of the above general formula (I) having as central unit a 1H-imidazol-1,5-diyl moiety include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-5-(trifluorometliyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-2-fluoropyridine 1-oxide, 2-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-6-methylpyridine 1-oxide, and 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-6-methylpyridine 1-oxide.

[0028] Described are compounds of the above general formula (I) having as central unit a isoxazol-3,5-diyl moiety include 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4-(trifiuorornethyl)pyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-fluoropyridine 1-oxide, 4-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-fluoropyridine 1-oxide, 2-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-4,6-dimethylpyridine 1-oxide.

[0029] Described are compounds of the above general formula (I) having as central unit a carbonyl moiety include 3-(3,4-dihydroxy-5-nitrobenzoyl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(3,4-dihydroxy-5-nitrobenzoyl)-4,6-dimethylpyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(3,4-dihydroxy-5-nitrobenzoyl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(3,4-dihydroxy-5-nitrobenzoyl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(3,4-dihydroxy-5-nitrobenzoyl)pyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(3,4-dihydroxy-5-nitrobenzoyl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(3,4-dihydroxy-5-nitrobenzoyl)-4,5,6-trimethylpyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(3,4-dihydroxy-5-nitrobenzoyl)-4,6-dimethylpyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(3,4-dihydroxy-5-nitrobenzoyl)-2-fluoropyridine 1-oxide, 4-(3,4-dihydroxy-5-nitrobenzoyl)-2-fluoropyridine 1-oxide, 2-(3,4-dihydroxy-5-nitrobenzoyl)-6-fluoropyridine 1-oxide, 2-chloro-3-(3,4-dihydroxy-5-nitrobenzoyl)-6-methylpyridine 1-oxide, 2-bromo-3-(3,4-dihydroxy-5-nitrobenzoyl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(3,4-dihydroxy-5-nitrobenzoyl)-4,6-dimethylpyridine 1-oxide.

[0030] Described are compounds of the above general formula (I) having as central unit an oxazol-2,4-diyl moiety include 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4-(trifluoromethyl)pyridine 1 -oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-fluoropyridine 1-oxide, 4-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-fluoropyridine 1-oxide, 2-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-6-fluoropyridine 1 -oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-4,6-dimethylpyridine 1-oxide.

[0031] Described are compounds of the above general formula (I) having as central unit an benzene- 1,3-diyl moiety include 3-(3',4'-dihydroxy-5'-nitrobiphenyl-3-yl)-4- (trifluoromethyl)pyridine 1-oxide, 5-(3',4'-dihydroxy-5'-nitrobiphenyl-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(3',4'-dihydroxy-5'-nitrobiphenyl-3-yl)pyridine 1-oxide, 3-(3',4'-dihydroxy-5'-nitrobiphenyl-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, and 3-(3',4'-dihydroxy-5'-nitrobiphenyl-3-yl)-5-(trifluoromethyl)pyridine 1-oxide.

[0032] Described are compounds of the above general formula (I) having as central unit an 1-H-pyrazol-1,5-diyl moiety include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1 H-pyrazol-1-yl)-4-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1 H-pyrazol-1-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-pyrazol-1-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1 H-pyrazol-1-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-pyrazol-1-yl)-5-(trifluoromethyl)pyridine 1-oxide, and 4-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-pyrazol-1-yl)-2-fluoropyridine 1-oxide.

[0033] Described are compounds of the above general formula (I) having as central unit an pyrimidin-2,4-diyl moiety include 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidn-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-4,6-dimethylpyridine 1-oxide, and 3-(4-(3,4-dihydroxy-5-nitrophenyl)pyrimidin-2-yl)-5-(trifluoromethyl)pyridine 1-oxide.

[0034] Described are compounds of the above general formula (I) having as central unit an 1 H-pyrrol-2,5-diyl moiety include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-3-(ethoxycarbonyl)-1 H-pyrrol-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1 H-pyrrol-2-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1-ethyl-3-(ethoxycarbonyl)-1 H-pyrrol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1 H-pyrrol-2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1 H-pyrrol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-2-fluoropyridine 1-oxide, 4-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1 H-pyrrol-2-yl)-2-fiuoropyridine 1-oxide, 2-(5-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)-1-methyl-1 H-pyrrol-2-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-1H-pyrrol-2-yl)-4,6-dimethylpyridine 1-oxide.

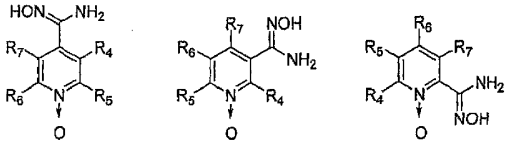
[0035] Described are compounds of the above general formula (I) having as central unit an 2H-tetrazol-2,5-diyl moiety include 3-(5-(3,4-dihydroxy-5-nitrophenyl)-2H-tetrazol-2-yl)-4-(trifluoromethyl)pyridine 1-oxide, 5-(5-(3,4-dihydroxy-5-nitrophenyl)-2H-tetrazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(5-(3,4-dihydroxy-5-nitrophenyl)-2H-tetrazol-2-yl)pyridine 1-oxide, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-2H-tetrazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, and 3-(5-(3,4-dihydroxy-5-nitrophenyl)-2H-tetrazol-2-yl)-5-(trifluoromethyl)pyridine 1-oxide.

[0036] Described are compounds of the above general formula (I) having as central unit an 1,2,3-thiadiazol-4,5-diyl moiety include 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4-(trifiuoromethyl)pyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-methyl-6-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-(trifiuoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4,5,6-trimethylpyridine 1-oxide,

2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-fluoropyridine 1-oxide, 4-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-2-fluoropyridine 1-oxide, 2-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-6-methylpyridine 1-oxide, and 2-bromo-5-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,2,3-thiadiazol-5-yl)-4,6-dimethylpyridine 1-oxide.

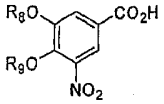
[0037] Described are compounds of the above general formula (I) having as central unit an thiazol-2,4-diyl moiety include 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-4-trifluoromethyl)pyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-2-methyl-6-(trifluoromethyl)pyridine-1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 5-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)- 2-methyl-4-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol- 2-yl)-2,6-dimethyl-4-(trifluoromethyl)pyridine 1-oxide, 3,5-dichloro-4-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)pyridine 1 -oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazof-2-yl)-6-methyl-2-phenyl-4-(trifluoromethyl)pyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-4,5,6-trimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 2,5-dichloro-3-(4-(3,4- dihydroxy-5-nitrophenyl)thiazol-2-yl)-4,6-dimethylpyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-5-(trifluoromethyl)pyridine 1-oxide, 3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-2-fluoropyridine 1 -oxide, 4-(4-(3 ,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-2-fluoropyridine 1-oxide, 2-(4-(3,4-dihydroxy-5- nitrophenyl)thiazol-2-yl)-6-fluoropyridine 1-oxide, 2-chloro-3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-6-methylpyridine 1-oxide, 2-bromo-3-(4-(3,4-dihydroxy-5-nitrophenyl)thiazol-2-yl)-6-niethylpyridine 1-oxide, and 2-bromo-5-chloro-3-(4-(3,4- dihydroxy-5-nitrophenyl)thiazol-2-yl)-4,6-dimethylpyridine 1-oxide.

[0038] In one instance, compounds of the general formula I wherein the central unit consists of a 1,2,4-oxadiazo-3,5-diyl-moiety can be prepared by a process wherein a compound of the general formula IIA, IIB or IIC,



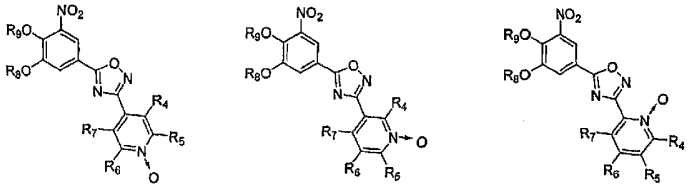
IIA IIB IIC

wherein R_4, R_5, R_6 and R_7 are defined as in the general formula I, is subjected to a cyclisation reaction comprising condensation and dehydration with a compound of the general formula III,



(III),

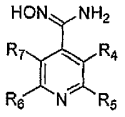
wherein R_8 and R_9 independently from each other represent hydrogen or suitable protective groups for aromatic hydroxyl groups, under conditions suitable to produce oxadiazole derivatives of formula IVA, IVB or IVC,



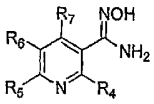
IVA IVB IVC

followed by removal of the hydroxyl protecting groups to provide the compounds of general formula I wherein the central unit consists of a 1,2,4-oxadiazo-3,5-diyl-moiety.

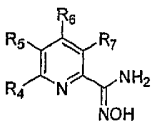
[0039] In another instance, the compounds of the general formula I wherein the central unit consists of a 1,2,4-oxadiazo-3,5-diyl-moiety can be prepared by a process wherein a compound of the general formula VA, VB or VC,



VA

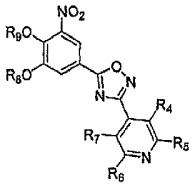


VB

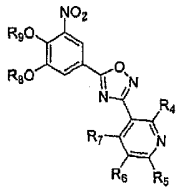


VC

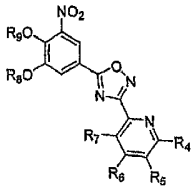
wherein R_4, R_5, R_6 and R_7 are defined as in the general formula I, is subjected to a cyclisation reaction comprising condensation and dehydration with a compound of the general formula III under conditions suitable to produce oxadiazole derivatives of formula VIA, VIB or VIC,



VIA



VIB



VIC

followed by oxidation of the pyridyl nitrogen atom to give a compound according to formula IVA, IVB or IVC as shown above and finally, if necessary, the removal of the hydroxyl protecting groups to provide the compounds of general formula I wherein the central unit consists of a 1,2,4-oxadiazo-3,5-diyl-moiety.

[0040] Suitable protective groups for aromatic hydroxyl groups are well known in the art. Examples of suitable protective groups for aromatic hydroxyl groups include methyl, ethyl, isopropyl, benzyl, 4-methoxybenzyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, tetrahydropyranyl, phenacyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, benzyloxycarbonyl, tert-butoxycarbonyl, ester, sulphonate, carbamate, phosphinate, acetal and ketal derivatives.

[0041] In one instance, one of the groups R_8 and R_9 is hydrogen and the other is methyl. In another instance, R_8 represents methyl and R_9 represents hydrogen.

[0042] The protective groups R_8 and R_9 may be replaced with hydrogen or a group which is hydrolysable under physiological conditions. The protective groups R_8 and R_9 may be removed independently from each other in separate reaction steps or they may be removed in the same reaction step. Likewise, the insertion of a group which is hydrolysable under physiological conditions may take place either in the same or in a subsequent reaction step.

[0043] In the present disclosure, conditions suitable to produce oxadiazole derivatives comprise conditions which give the oxadiazole derivative in high yield and purity. Preferably, the yield of the desired oxadiazole derivative is at least 70%, more preferably 75 to 99%, even more preferably 80 to 97%, and most preferably 85 to 95%. Preferably, the purity of the desired oxadiazole derivative is at least 90%, more preferably at least 95%, even more preferably at least 99%, and most preferably at least 99.5%. Following the teaching of the present invention the skilled person can routinely determine the most suitable reaction conditions in order to optimize the yield and purity of the oxadiazole. Parameters to be taken into consideration by the skilled person include, but are not limited to, reagents effecting the condensation and dehydration agents, choice of protective groups R_8 and R_9, solvent system, reaction temperature and reaction time and solubility of reagents.

[0044] The compound of general formula III requires activation before condensation with a compound of formula IIA-IIC or VA-VC. Suitable reagents for activation of the compound of formula III include 1,1-carbonyldiimidazole, thionyl chloride, sulfonylchloride, N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, phosgene, PCl_3, $POCl_3$, PCl_5, anhydrides, trichlorotriazine and chlorodimethoxytriazine and the like. Particularly preferable are 1,1-carbonyldiimidazole and thionyl chloride. In some cases, the same reagents can be employed to effect the cyclisation step, which consists of condensation and dehydration. Alternative reagents to effect condensation and/or dehydration include pyridine and tetrabutylammonium fluoride. Preferably the dehydration can be effected by thermal heating of the reaction mixture in conjunction with the aforementioned reagents.

[0045] The compound of general formula III can be activated with an excess of a reagent such as thionyl chloride in a suitable solvent or without the need for additional solvent. If preferred, the excess reagent can then be removed, e.g. by distillation, and replaced with a solvent and another reagent such as pyridine to effect the condensation and dehydration steps. Preferred solvent systems for activating the compound of general formula III, and cyclisation with compounds of general formulas IIA-IIC or VA-VC are dipolar aprotic solvents including dimethylformamide, dimethylsulfoxide, dimethylacetamide and N-methylpyrrolidinone. Particularly preferable are dimethylsulfoxide and dimethylacetamide.

[0046] Suitable reaction temperatures and reaction times depend on the reactivity of the utilized reagents for effecting condensation and dehydration. Preferably, the reaction temperature is in the range of 0°C to the boiling point of the utilized solvent system, more preferably in the range of 20 to 150°C, and most preferably in the range of 25 to 120°C, Preferably, the reaction time is in the range of 30 minutes to 24 hours, more preferably in the range of 1 hour to 18 hours, and most preferably 2 to 6 hours.

[0047] In an alternative instance, the condensation and dehydration reaction is carried out in the presence of an organic or inorganic base. Suitable preferred bases include triethylamine, tributylamine, 2,6-lutidine, N-methylmorpholine, pyridine, imidazole, N-methylimidazole and 4-dimethylaminopyridine. Particularly preferred bases include pyridine, N-methylimidazole and 4-dimethylaminopyridine.

[0048] In another instance, the condensation and dehydration are conducted in two separate reaction steps. In this particular embodiment, different condensation and dehydration agents and solvent systems may be utilized to optimize yield and purity of the obtained product.

[0049] In yet another instance, the condensation and dehydration are conducted sequentially in the same vessel without isolation of the O-acylated intermediates. In this particular instance, the reagents effecting the condensation and dehydration can be the same or different but are preferably identical.

[0050] The amount of reagents effecting the condensation and dehydration are not critical. Typical amounts of reagents effecting the condensation and dehydration include at least an amount of 1 mol, preferably 2.1 mol to 5 mol, more preferably 2.2 to 4 mol, and most preferably 2.3 mol to 3 mol, per mol pyridine derivative. In cases in which the reagents effecting the condensation and dehydration also serves as solvent or co-solvent, the excess amount may be much higher.

[0051] As mentioned above, the invention may include a step in which the nitrogen atom of the pyridyl moiety VIA, VIB or VIC is oxidized under suitable conditions to the corresponding pyridyl-N-oxide derivative IVA, IVB or IVC after the cyclisation reaction.

[0052] In the present disclosure, suitable oxidative conditions to produce the pyridyl-N-oxide comprise conditions which give the pyridyl-N-oxide derivative in high yield and purity

[0053] Preferably, the yield of the desired pyridyl-N-oxide derivative is at least 90%, more preferably 92 to 99%, even more preferably 94 to 98%, and most preferably 95 to 97%. Preferably, the purity of the desired pyridyl-N-oxide derivative is at least 90%, more preferably at least 95%, even more preferably at least 99%, and most preferably at least 99.5%. Following the teaching of the present invention the skilled person can routinely determine the most suitable reaction conditions in order to optimize the yield and purity of the pyridyl-N-oxide. Parameters to be taken into consideration by the skilled person include, but are not limited to, oxidizing agent, amount of oxidizing agent, choice of protective groups, solvent system, reaction temperature and reaction time and solubility of reagents.

[0054] Preferred oxidizing agents include hydrogen peroxide, MnO_2, peracetic acid, trifluoroperacetic acid, t-butylhydroperoxide, m-chloroperoxybenzoic acid, persulfuric acids, Oxone®, urea hydrogen peroxide complex and trifluoroacetic anhydride, pyridinium chlorochromate and permanganate ions. Particularly preferred is urea hydrogen peroxide complex and trifluoroacetic anhydride.

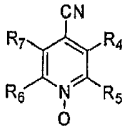
[0055] The preferred amount of oxidizing agent is in the range of equimolar amounts to a 20-fold excess to the pyridine derivative. Preferably, amount of oxidizing agent is in the range of a 1.2- fold to 10-fold excess, more preferably 1.5-fold to 8-fold excess and most preferably 2-fold to 5-fold excess.

[0056] Preferred solvent systems for conducting the oxidation are solvents which are inert to the oxidizing agent. Particularly preferred are halogenated solvents, such as dichloromethane, chloroform, chlorobenzene and carbon tetrachloride, aromatic solvents such as benzene and toluene, alkanes such as cyclohexane and hexane, and ethers such as THF, 1,4-dioxane and tert-butylmethylether.

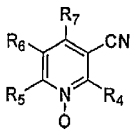
[0057] Suitable reaction temperatures and reaction times depend on the reactivity of the utilized oxidizing agent. Preferably, the reaction temperature is in the range of 0°C to the boiling point of the utilized solvent system, more preferably in the range of 20 to 100°C, and most preferably in the range of 40 to 80 °C. Preferably, the reaction time is in the range of 30 minutes to 24 hours, more preferably in the range of 1 hour to 18 hours, and most preferably 2 to 6 hours.

[0058] The oxidation of the pyridyl nitrogen atom can be carried out at any stage of the process of preparation of compounds according to the general formula I. Preferably, the oxidation is conducted before formation of the compounds of formulae IIA-IIC, or alternatively after formation of the oxadiazole ring as in compounds of formulae VIA-VIC.

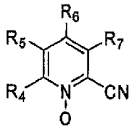
[0059] In another instance, compounds of formula IIA, IIB or IIC are prepared by reacting compounds of the general formula VIIA, VIIB or VIIC,



VIIA



VIIB



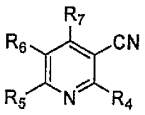
VIIC

with hydroxylamine in the presence of a chelating agent under suitable reaction conditions.

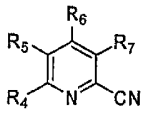
[0060] In another instance, compounds of formula VA, VB or VC are prepared by reacting compounds of the general formula VIIIA, VIIIB or VIIIC,



VIIIA



VIIIB



VIIIC

with hydroxylamine in the presence of a chelating agent under suitable reaction conditions.

[0061] In the present disclosure, suitable reaction conditions of the above reactions comprise conditions which give the amidoxime derivative in high yield and purity. Preferably, the yield of the desired amidoxime derivative is at least 70%, more preferably 72 to 95%, even more preferably 75 to 90%, and most preferably 78 to 85%. Preferably, the purity of the desired amidoxime derivative is at least 90%, more preferably at least 95%, even more preferably at least 96%, and most preferably at least 97%. Following the teaching of the present disclosure the skilled person can routinely determine the most suitable reaction conditions in order to optimize the yield and purity of the amidoxime. Parameters to be taken into consideration by the skilled person include, but are not limited to, amount of hydroxylamine, choice of catalyst, nature of substituents R_4 to R_7, solvent system, reaction temperature and reaction time and solubility of reagents.

[0062] The preferred amount of hydroxylamine is in the range of equimolar amounts to a 50-fold excess to the pyridine derivative. Preferably, the amount of hydroxylamine is in the range of a 1.2- fold to 20-fold excess, more preferably 1.5-fold to 10-fold excess and most preferably 3-fold to 5-fold excess.

[0063] Preferred chelating agents include 8-hydroxyquinoline, ortho-phenanthroline and hydrates and derivatives thereof. The preferred amount of chelating agent is in the range 0.1-10 mol%, more preferably 0.5-5 mol%, more preferably 0.75-3 mol% and most preferably 1- 1.5 mol%.

[0064] The solvent system is not particularly limited and includes water, alcohols such as methanol, ethanol or isopropanol, ethers such as THF or 1,4-dioxane, and dipolar aprotic solvents, such as dimethylsulfoxide and the like or mixtures of these solvents.

[0065] Preferably, the reaction temperature is in the range of 0°C to the boiling point of the utilized solvent system, more preferably in the range of 20 to 100°C and most preferably in the range of 40 to 80°C. Preferably, the reaction time is in the range of 30 minutes to 24 hours, more preferably in the range of 1 hour to 18 hours, and most preferably 2 to 8 hours.

[0066] For the preparation of pharmaceutical compositions of general formula (I), inert pharmaceutically acceptable carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules and capsules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

[0067] Preferably, the pharmaceutical preparation is in unit dosage form, e.g. packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampoules.

[0068] The dosages may be varied depending on the requirement of the patient, the severity of the disease and the particular

compound being employed. For convenience, the total daily dosage may be divided and administered in portions throughout the day. Determination of the proper dosage for a particular situation is within the skill of those in the medical art.

Materials and Methods

Assay of mouse COMT activity

[0069] Liver samples from 60 days old NMRI mice weighing 20-30 g (Harlan-Interfauna Ibérica, Barcelona, Spain) kept ten per cage under controlled environmental conditions (12 h light/dark cycle and room temperature 24 °C), were used in all experiments. Saline perfused tissues, obtained from pentobarbitone (60 mg/kg) anaesthetised mice, were used in the experiments. Tissues were immediately removed and homogenised in 5 mM phosphate buffer, pH 7.8 and stored at -80 °C.

[0070] COMT activity was evaluated by the ability to methylate adrenaline to metanephrine, as previously described (Vieira-Coelho, M.A., Soares-da-Silva, P., Brain Res, 1999, 821, 69-78). Aliquots of 0.5 ml of liver homogenates were preincubated for 20 min with 0.4 ml of phosphate buffer (5 mM); thereafter, the reaction mixture was incubated for 10 min with adrenaline (500 µM; 0.1 ml) in the presence of a saturating concentration of S-adenosyl-L-methionine, the methyl donor (250 µM). The incubation medium also contained pargyline (100 µM), $MgCl_2$ (100 µM) and EGTA (1 mM). The preincubation and incubation were carried out at 37 °C under conditions of light protection with continuous shaking and without oxygenation. At the end of the incubation period the tubes were transferred to ice and the reaction was stopped by the addition of 200 µl of 2 M perchloric acid. The samples were then centrifuged (200 x g, 4 min, 4 °C), and 500 µl aliquots of the supernatant, filtered on 0.22 µm pore size Spin-X filter tubes (Costar) were used for the assay of metanephrine by high pressure liquid chromatography with electrochemical detection.

[0071] In experiments designed to evaluate the effects of test compounds upon liver COMT, test compounds (in 0.5% carboxymethylcellulose) were given by gastric tube to overnight fasted mice. Thereafter, at defined intervals, livers were removed and used to determine COMT activity as described above. Where applicable, blank solutions containing 0.5% carboxymethylcellulose were used as control.

Assay of rat COMT activity

[0072] Livers from 60 day old male Wistar rats weighing 240-260 g (Harlan-Interfauna Ibérica, Barcelona, Spain), kept two per cage under controlled environmental conditions (12 h light/dark cycle and room temperature 24 °C) were used in all experiments. After decapitation, the organs were immediately removed and homogenised in 5 mM phosphate buffer of pH 7.8. COMT activity was evaluated by the ability to methylate adrenaline to metanephrine. Aliquots of 0.5 ml of liver homogenates were preincubated for 20 min with 0.4 ml of phosphate buffer (5 mM); thereafter, the reaction mixture was incubated for 5 min with epinephrine (1000 µM; 0.1 ml) in the presence of a saturating concentration of S-adenosyl-L-methionine (500 µM), the methyl donor; the incubation medium contained also pargyline (100 µM), $MgCl_2$ (100 µM) and EGTA (1 mM). The preincubation and incubation were carried out at 37 °C under conditions of light protection with continuous shaking and without oxygenation.

[0073] In experiments designed to evaluate the oral bioavailability of test substances, compounds were given by gastric tube to overnight fasted rats. Thereafter, at defined intervals, animals were killed by decapitation and livers removed and used to determine COMT activity as described above. At the end of the incubation period (5 min) the tubes were transferred to ice and the reaction was stopped by the addition of 200 µl of 2 M perchloric acid. The samples were then centrifuged (200xg, 4 min, 4 °C), and 500 µl aliquots of the supernatant, filtered on 0.22 µm pore size Spin-X filter tubes (Costar) were used for the assay of metanephrine. The assay of metanephrine was carried out by means of high pressure liquid chromatography with electrochemical detection. The lower limits for detection of metanephrine ranged from 350 to 500 fmol (0.5 to 1.0 pmol/mg protein/h).

Levels of L-DOPA and 3-O-methyl-L-DOPA in plasma

[0074] Rats fasted overnight were administered orally with tolcapone, entacapone and compounds of general formula I (all at 3 mg/kg) or vehicle (0.5% carboxymethylcellulose, 4 ml/kg). One, 6 or 23 h later, rats were administered orally with L-DOPA (12 mg/kg) plus benserazide (3 mg/kg) or with vehicle (0.5% carboxymethylcellulose, 4 ml/kg). One hour later rats were anaesthetised

with sodium pentobarbitone (60 mg/kg, i.p.), blood was collected through the vena cava and the whole brain was quickly removed. Blood samples were centrifuged for 15 min at 3,000 g (4 °C) and the plasma samples were stored at -80 °C till the assay of L-DOPA and 3-O-methyl-L-DOPA. All animals interventions were performed in accordance with the European Directive number 86/609, and the rules of the "Guide for the Care and Use of Laboratory Animals", 7th edition, 1996, Institute for Laboratory Animal Research (ILAR), Washington, DC.

Assay of L-DOPA and catechol derivatives

[0075] L-DOPA and 3-O-methyl-L-DOPA in blood samples were assayed by HPLC with electrochemical detection, as previously described (Soares-da-Silva et al., Brain Res. 2000;863:293-297). In brief, aliquots of 20 µl were injected into the chromatograph. The chromatographic system consisted of a pump (Gilson 307) and a stainless steel 5 µm ODS2 column (Biophase; Bioanalytical Systems, West Lafayette, IN) of 25 cm length and 4.6 mm diameter; samples were injected by means of an automatic sample injector (Gilson 231) connected to a Gilson dilutor (Gilson 401). The mobile phase was a degassed solution of citric acid 0.1 mM; sodium octylsulphate 0.5 mM; sodium acetate 0.1 M; Na_2EDTA 0.17 mM; dibutylamine 1 mM and methanol (10% v/v), adjusted to pH 3.5 with PCA 2 M and pumped at a rate of 1.0 ml min^{-1}. The detection was carried out electrochemically with a glassy carbon electrode, an Ag/AgCl reference electrode and an amperometric detector (Gilson 142); the detector cell was operated at 0.75 V. The current produced was monitored using the Gilson Unipoint HPLC software.

Cell toxicity

[0076] The method, which detects cell toxicity of a test substance, follows that described by Pedrosa and Soares-da-Silva (Br. J. Pharmacol., 137, 1 1305-1313, 2002). Briefly, Neuro 2A mouse neuroblastoma cells were seeded in 96-well plates in 200 µL per well of culture medium for cell attachment (CMA), under a CO_2/air (5%/95%) humidified atmosphere at 37 °C. Controls of the test system prior to incubations consisted in a morphological control (light microscopy) of the cultured cells: attachment, spreading and density. Five days after seeding (24 h after cells become confluent), the test compounds were incubated for 24 h with cultured cells. Cultures with no test article or ethanol were run in parallel as negative and positive controls. All incubations contained the same percentage of solvent needed for the test compound.

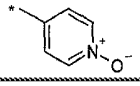
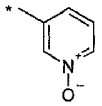
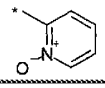
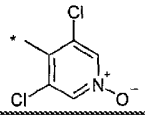
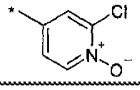
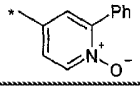
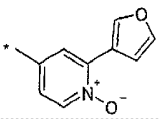
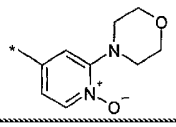
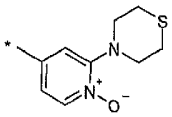
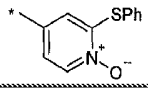
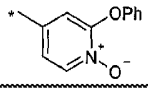
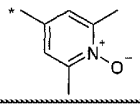
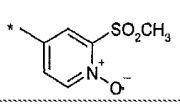
[0077] Cell viability was measured using calcein-AM (Molecular Probes, Eugene, OR, USA). The membrane permeant calcein-AM, a nonfluorescent dye, is taken up and converted by intracellular esterases to membrane impermeant calcein, which emits green fluorescence. After treatment with test article or vehicle for 24 h, cells are washed twice with Hanks' medium (medium composition, in mM: NaCl, 137; KCl, 5; $MgSO_4$, 0.8; Na_2HPO_4, 0.33; KH_2PO_4, 0.44; $CaCl_2$, 0.25; $MgCl_2$, 1.0; Tris HCl, 0.15 and sodium butyrate, 1.0, pH=7.4) and loaded with 2 µM calcein-AM in Hanks' medium, at room temperature for 30 min. Fluorescence is measured at 485 nm excitation and 530 nm emission wavelengths in a multiplate reader. To determine minimum staining for calcein-AM (calceinmin), eight wells were treated with ethanol 30 min before calcein-AM addition. The percent viability is then calculated as $[(calcein_{sample} - calcein_{min}) / (calcein_{control} - calcein_{min})] \times 100$.

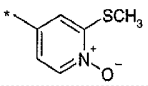
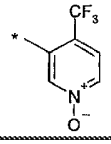
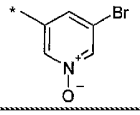
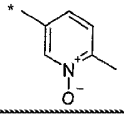
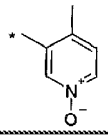
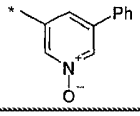
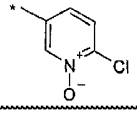
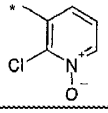
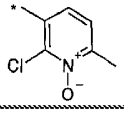
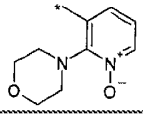
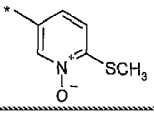
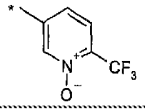
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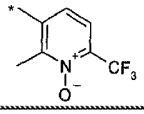
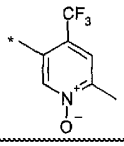
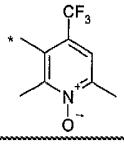
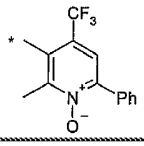
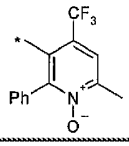
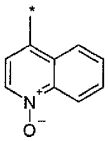
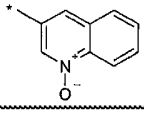
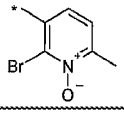
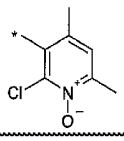
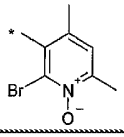
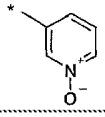
[0078] Table 1 shows the effects of standard COMT inhibitors, tolcapone and entacapone, and compounds of general formula I upon mouse liver COMT activity 3 h after their oral administration (3 mg/kg). Also shown in table 1 is the cell viability after 24 h expsoure to tolcapone, entacapone and compounds of general formula I (all at 30 µM) in Neuro 2A cells.

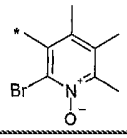
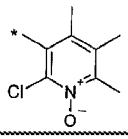
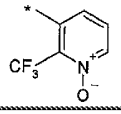
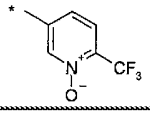
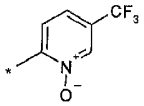
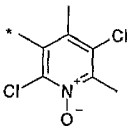
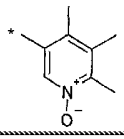
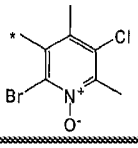
Table 1. Mouse Liver COMT activity (% control) after 3 mg/kg (oral) administration of compounds listed and Neuro 2A cell viability (% of viable cells)

No.	(X)n, (Y)n	R3	COMT activity (% of control)	% of viable cells
Tolcapone			13.9	27.2
Entacapone			79.8	81.4
1	n = m = 0	$-CH_3$	59.9	55.1
2	n = m = 0	$-CH_3$	78.8	92.5
3	n = m = 0	$-CH_3$	63.6	100.5

No.	(X)n, (Y)n	R3	COMT activity (% of control)	% of viable cells
4	n = m = 0		42.1	98.3
5	n = m = 0		58.4	93.8
6	n = m = 0		101.0	107.1
7	n = m = 0		14.2	56.9
8	n = m = 0		55.4	106.7
9	n = m = 0		80.6	79.7
10	n = m = 0		95.2	69.3
11	n = m = 0		63.9	105.7
12	n = m = 0		92.9	91.7
13	n = m = 0		102.3	
14	n = m = 0		76.8	83.5
15	n = m = 0		79.2	97.1
16	n = m = 0		85.9	64.6

No.	(X)n, (Y)n	R3	COMT activity (% of control)	% of viable cells
17	n = m = 0		89.9	96.0
18	n = m = 0		21.2	93.4
19	n = m = 0		45.2	100.1
20	n = m = 0		56.6	
21	n = m = 0		95.6	
22	n = m = 0		111.6	
23	n = m = 0		43	41.1
24	n = m = 0		71.8	93.7
25	n = m = 0		23.1	100.2
26	n = m = 0		35.5	110.9
27	n = m = 0		47.5	95.7
28	n = m = 0		11.3	87.0

No.	(X)n, (Y)n	R3	COMT activity (% of control)	% of viable cells
29	n = m = 0		10.9	62.2
30	n = m = 0		8.8	81.8
31	n = m = 0		0.8	37.2
32	n = m = 0		9.7	26.6
33	n = m = 0		39.8	45.0
34	n = m = 0		88.6	89.0
35	n = m = 0		81.2	88.0
36	n = m = 0		22.9	76.3
37	n = m = 0		42.5	92.3
38	n = m = 0		16.3	86.0
39	X=CH2, n=1, m=0		53.8	94.9

No.	(X)n, (Y)n	R3	COMT activity (% of control)	% of viable cells
40	n = m = 0		55.2	69.1
41	n = m = 0		14	95.1
42	n = m = 0		9.4	96.4
43	X-CH2, n=1, m=0		27.2	101.5
44	X = CH2, n =1 Y = O , m = 1		24.5	
45	n = m = 0		30.4	86.6
46	n = m = 0		43.1	53.0
47	n = m = 0		25.2	81.2
Note: * represents the point of attachment of the pyridine N-oxide substituent to the molecule				

[0079] Compounds of general formula I were also found to be potent inhibitors of rat liver COMT, the maximal inhibitory effect being achieved within 1 h to 3 h after their oral administration (Table 2). The maximal inhibitory effect of entacapone (Ent) and tolcapone (Tolc) were observed within 1 h after administration (Table 2). Nine hours after administration, entacapone is devoid of COMT inhibitory effects and tolcapone produces minimal inhibitory effects (~ 16% inhibition), whereas compounds of general formula I continue to inhibit COMT activity by 22% to 90% of control levels (Table 2).

Table 2. Rat Liver COMT activity (% control) after 3 mg/kg (oral) administration of compounds listed.

	Time (h)			
Compound	1	3	6	9
Entacapone	32.0	74.5	95.2	100.0
Tolcapone	18.3	28.6	56.8	83.9
18	5.2	19.9	43.0	57.4

	Time (h)			
Compound	1	3	6	9
29	1.2	18.5	39.7	56.4
30	6.3	34.8	41.2	54.5
41	21.2	9.3	18.8	39.7
42	3.6	6.1	12.3	30.9
43	16.1	30.6	64.3	77.9
45	1.1	1.2	3.8	8.9
47	10.6	4.0	3.8	8.2

[0080] Table 3 shows percentage changes in plasma levels of L-DOPA and 3-O-methyl-L-DOPA (3-OMD) of rats treated with L-DOPA plus benserazide at 2 h after the administration of entacapone, tolcapone and compounds of general formula I (3 mg/kg). L-DOPA plus benserazide were administered 1 h before collection of plasma samples. This time-point was chosen because it represented the t_{max} for L-DOPA. As can be observed, compounds of general formula I produced significant increases in plasma L-DOPA accompanied by marked decrease in plasma 3-O-methyl-L-DOPA.

Table 3. Effect of of compounds listed (3 mg/kg; oral administration) upon changes (% control) in plasma levels of L-DOPA and 3-O-methyl-L-DOPA (3-OMD) of rats treated with L-DOPA plus benserazide.

Compound	L-DOPA % increase	3-OMD % reduction	L-Dopa / 3-OMD
Entacapone	68.5	-55.6	3.8
Tolcapone	202.4	-89.0	27.6
18	61.4	-63.9	4.5
29	105.1	-80.7	10.6
30	103.5	-75.0	8.1
41	95.2	-72.3	7.1
42	30.7	-43.4	2.3
43	74.9	-48.3	3.4
45	100.8	-54.3	4.4
47	102.9	-58.5	4.9

Conclusion

[0081] Compounds of general formula I are very potent catechol-O-methyltransferase (COMT) inhibitors with significantly reduced toxicity. Compounds of general formula I have potentially valuable pharmaceutical properties in the treatment of some central and peripheral nervous system disorders where inhibition of O-methylation of catecholamines may be of therapeutical benefit, such as mood disorders, Parkinson's disease and parkinsonian disorders, restless legs syndrome, gastrointestinal disturbances, edema formation states and hypertension. The possibility to use a potent, long-acting inhibitor with improved safety profile opens new perspectives in the treatment of Parkinson's disease and parkinsonian disorders, gastrointestinal disturbances, edema formation states, and hypertension by improving the safety of nitrocatecholic COMT inhibitors whilst improving or maintaining duration and selectivity of COMT inhibition. This is particularly important when thinking of treating patients afflicted by Parkinson's disease who are taking L-DOPA plus a peripheral AADC inhibitor due to the fact that this is long-term treatment.

[0082] The invention disclosed herein is exemplified by the following examples and comparative examples of preparation, which should not be construed to limit the scope of the disclosure. Alternative pathways and analogous structures may be apparent to those skilled in the art.

Example 1

3-Nitro-5-[3-(1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol (compound 4, Table 1)

[0083]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (0.5 g, 1.32 mmol) in dimethylformamide (5 mL) at room temperature was added 1,1-carbonyldiimidazole (0.246 g, 1.52 mmol) in one portion. After stirring for one hour, N'-hydroxypyridine-4-carboximidamide (0.208 g, 1.52 mmol) was added in one portion and the resulting mixture was stirred at room temperature overnight. The mixture was then stirred at 110°C for three hours and then allowed to cool to room temperature. The mixture was poured onto ice-water (100 mL) and extracted with 20% isopropanol/dichloromethane. The organic extracts were washed with water and brine, then dried (Na_2SO_4), filtered and evaporated to leave a solid residue that was recrystallised from ethanol. 4-[5-(3,4-Bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-pyridine was obtained as a beige solid (0.395 g, 62%).
2. b) A stirred solution of the above pyridine compound (0.331 g, 0.689 mmol) in dichloromethane (15 mL) was cooled in an ice- water bath and m-chloroperoxybenzoic acid (0.179 g, 1.03 mmol) was added in portions. The resulting mixture was stirred in the cold for thirty minutes and then at room temperature for thirty minutes whereupon it was cooled again in an ice-water bath. Further m-chloroperoxybenzoic acid (0.17 g, 1.03 mmol) was added and the mixture was then allowed to stir at room temperature for one and a half hours. Water (20 mL) was added and the organic phase was separated and washed with saturated aqueous sodium bicarbonate solution, water and brine, then dried (Na_2SO_4), filtered and evaporated to leave a yellow oil. Addition of diethyl ether caused formation of a precipitate that was filtered off and recrystallised from a dichloromethane/isopropanol mixture. 4-[5-(3,4-Bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-pyridine 1-oxide was obtained as white crystals (0.239 g, 70%).
3. c) A solution of the above dibenzyl ether (0.232 g, 0.468 mmol) in dichloromethane (5 mL) was cooled to -78 °C with stirring under argon and treated with boron tribromide (0.586 g, 2.34 mmol) dropwise. The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -78 °C. The mixture was quenched by the careful addition of methanol. After stirring at room temperature for one hour, the volatiles were evaporated and the residue treated with ethanol/toluene and re-evaporated. The yellow residue was triturated with boiling ethanol and filtered whilst still warm to give the title product as a yellow solid (0.102 g, 69%) of m.p. 280-282 °C.

Example 2

3- Nitro-5-[3-(l-oxy-pyridin-3-yl)-[1,2,4] oxadiazol-5-yl]-benzene-1,2-diol (compound 5, Table 1)

[0084]

1. a) To a stirred solution of 3,4-dimethoxy-5-nitrobenzoic acid (0.232 g, 1.022 mmol) in dimethylformamide (5 ml) at room temperature was added 1,1-carbonyldiimidazole (0.174 g, 1.073 mmol) in one portion. The resulting mixture was stirred for ninety minutes whereupon N'-hydroxypyridine-3-carboximidamide 1-oxide (0.156 g, 1.022 mmol) was added in one portion. The resulting mixture was stirred at room temperature for two hours, then at 75 °C overnight. After cooling to room temperature, the mixture was poured onto water (100 mL) and the precipitate was filtered off, washed with water, then dried in air and recrystallised from diethyl ether. 3-[5-(3,4-dimethoxy-5-nitro-phenyl-[1,2,4]oxadiazol-3-yl]-pyridine 1-oxide was obtained as a white solid (0.162 g, 46%).
2. b) To a stirred solution of the dimethyl ether from above (0.153 g, 0.445 mmol) in dichloromethane (10 mL) at -78 °C under argon was added boron tribromide dropwise (0.445 g, 1.779 mmol). The reaction mixture was allowed to warm to room temperature and stirred for ninety minutes before pouring carefully onto water (100 mL). After stirring for twenty minutes, the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated. 2-methoxy-3-nitro-5-[3-(1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-phenol was obtained as a yellow solid (0.12 g, 82%).
3. c) A stirred suspension of the above methyl ether (0.108 g, 0.327 mmol) in 1,2-dichloroethane (10 mL) at room temperature under argon was treated with aluminium chloride (0.087 g, 0.654 mmol) followed by pyridine (0.207 g, 2.62 mmol) dropwise. The mixture was then heated at reflux for seven hours whereupon further aluminium chloride (0.087 g, 0.654 mmol) and pyridine (0.207 g, 2.62 mmol) were added and the mixture stirred at reflux for a further seven hours. The mixture was then allowed to cool to room temperature, and poured onto cold 1 N hydrochloric acid (30 mL). The resulting

precipitate was filtered off, washed with water and dried at 50 °C under vacuum. The desired product was obtained as an orange solid, (0.075 g, 72%) of m.p. 278-280 °C.

Example 3

3-Nitro-5-[3-(1-oxy-pyridin-2-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol (compound 6, Table 1)

[0085]

1. a) To a stirred solution of 3,4-dimethoxy-5-nitrobenzoic acid (1.0 g, 4.40 mmol) in dimethylformamide (10 mL) at room temperature was added 1,1-carbonyldiimidazole (0.821 g, 5.06 mmol) in one portion. The resulting yellow mixture was allowed to stir for ninety minutes whereupon N'-hydroxypyridine-2-carboximidamide 1-oxide (0.775 g, 5.06 mmol) was added in one portion. The resulting mixture was stirred at room temperature overnight and then poured onto water (100 mL). The resulting precipitate was filtered off, washed with water and then taken up in dichloromethane (30 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and evaporated to leave a white solid (1.37 g, 86%).
2. b) To a stirred suspension of the solid obtained above (1.365 g, 3.77 mmol) in tetrahydrofuran (14 mL) at room temperature under argon was added a 1 N solution of tetrabutylammonium fluoride in tetrahydrofuran (3.8 mL, 3.8 mmol). The resulting clear yellow solution was allowed to stir at room temperature for seven hours during which time a new precipitate had formed. The mixture was filtered and the solid was washed with several portions of cold tetrahydrofuran. 2-[5-(3,4-Dimethoxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-pyridine 1-oxide was obtained as a white solid (0.97 g, 75%).
3. c) To a stirred suspension of the dimethyl ether obtained from above (0.961 g, 2.79 mmol) in dichloromethane (15 mL) at -78 °C under argon was added boron tribromide (3.5 g, 13.97 mmol) dropwise. The resulting purple suspension was then allowed to stir at room temperature for seven hours before being cooled in an ice/water bath. The mixture was carefully quenched by the addition of methanol. The resulting yellow mixture was allowed to stir at room temperature for one hour before the precipitate was filtered off and washed with methanol. The solid was triturated with boiling ethanol and filtered whilst warm. After drying, the desired compound was obtained as an orange solid (0.712 g, 81%) of m.p. 168 °C.

Example 4

5-(5-Methyl-[1,2,4]oxadiazol-3-yl)-3-nitro-benzene-1,2-diol (compound 2, Table 1)

[0086]

1. a) To a stirred solution of 3,4-bis-benzyloxy-N'-hydroxy-5-nitro-benzamidine (1.0 g, 2.54 mmol) in dimethylformamide (5 mL) at room temperature was added 1,1-carbonyldiimidazole (0.494 g, 3.048 mmol) in one portion and the mixture was stirred at room temperature for ninety minutes. Thereupon, acetic acid (0.184 g, 3.067 mmol) was added dropwise and the mixture was allowed to stir for two hours at room temperature, then at 155 °C for three hours. The mixture was allowed to cool to room temperature, and poured onto ice-water (100 mL). Brine (10 mL) was added and the resulting precipitate was removed by filtration, washed with water and dried in air. The solid was then dissolved in dichloromethane (20 mL) and a spatula tip of activated charcoal was added. After stirring for twenty minutes, the suspension was filtered through celite and the filtrate was evaporated to leave a yellow oil that solidified on standing. After recrystallisation from dichloromethane/petroleum ether, 3-(3,4-bis-benzyloxy-5-nitrophenyl)-5-methyl-[1,2,4]oxadiazole was obtained as a pale yellow solid (0.537 g, 51%).
2. b) To a stirred solution of the solid obtained from above (0.128 g, 0.307 mmol) in dichloromethane (15 mL) at -78 °C under argon was added boron tribromide (0.318 g, 1.269 mmol) dropwise. The resulting purple suspension was allowed to stir at room temperature for one hour, then cooled again to -78 °C. The mixture was quenched by the careful addition of methanol, and after stirring at room temperature for one hour, the solvents were evaporated. The yellow residue was triturated with diethyl ether, filtered and dried. The desired compound was obtained as a yellow solid (0.070 g, 96%) of m.p. 169.8-172 °C.

Example 5

5-(5-Methyl-[1,3,4]oxadiazol-2-yl)-3-nitro-benzene-1,2-diol (compound 3, Table 1)

[0087]

1. a) To a stirred solution of 3,4-dimethoxy-5-nitrobenzoic acid (0.438 g, 1.93 mmol) in tetrahydrofuran (10 mL) at room temperature was added 1,1-carbonyldiimidazole (0.343 g, 2.12 mmol) in one portion and the mixture was stirred at room temperature for one hour, then at 70 °C for two hours, whereupon acetic hydrazide (0.157 g, 2.12 mmol) was added. The resulting was stirred at room temperature for thirty minutes, then at 70 °C for two hours. After cooling to room temperature, the mixture was poured onto ice-water (100 mL) and the precipitate was filtered off and washed with water. 3,4-Dimethoxy-5-nitro-benzoic acid N'-acetyl-hydrazide was obtained as a white solid (0.296 g, 54%).
2. b) A suspension of the solid obtained above (0.288 g, 1.017 mmol) in phosphorus oxychloride (7 mL) was stirred at 120 °C for two hours, then allowed to cool to room temperature. The solution was then poured onto ice-water (200 mL), causing formation of a white precipitate. Extracted with dichloromethane, and the organic extracts were washed with water and brine, then dried ,filtered and evaporated to leave a white solid. Recrystallisation from dichloromethane/petroleum ether gave 2-(3,4-dimethoxy-5-nitro-phenyl)-5-methyl-[1,3,4]oxadiazole as white crystals (0.151 g, 56%).
3. c) To a stirred solution of the solid obtained above (0.145 g, 0.547 mmol) in dichloromethane (10 mL) at -78 °C under argon was added boron tribromide (0.685 g, 2.74 mmol) dropwise. The resulting purple suspension was allowed to stir at room temperature overnight, then cooled again to -78 °C. The reaction was quenched by the addition of methanol, and after stirring at room temperature for one hour, the volatiles were evaporated. Toluene (20 mL) was added to the residue and re-evaporated. The residue was triturated with boiling ethanol and filtered whilst warm to give the desired product as an orange solid (0.107 g, 82%) of m.p. 245-246 °C.

Example 6

5-[3-(3,5-Dichloro-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol (compound 7, Table 1)

[0088]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (0.50 g, 1.32 mmol) in dimethylformamide (5 mL) at room temperature was added 1,1-carbonyldiimidazole (0.246 g, 1.52 mmol) in one portion, and the mixture was stirred for ninety minutes whereupon 3,5-dichloro-N'-hydroxy-1-oxyisonicotinamidine (0.337 g, 1.52 mmol) was added in one portion. The resulting mixture was stirred at room temperature overnight and then poured onto ice-water (100 mL). Brine (10 mL) was added and the precipitate was filtered off, washed with water and dissolved in 30% isopropanol/dichloromethane. The dichloromethane was then distilled off and the resulting isopropanol suspension was stored at 0 °C for one hour. The solid was then filtered off, washed with cold isopropanol and dried to leave a white solid (0.756 g, 98%).
2. b) A portion of this solid (0.664 g, 1.14 mmol) and 1,1-carbonyldiimidazole (0.185 g, 1.14 mmol) were dissolved in dimethylformamide (10 mL) was stirred at 100 °C for nine hours then at room temperature overnight. The resulting mixture was poured onto ice-water (100 mL) and then acidified to pH 1-2 by the dropwise addition of 2 N hydrochloric acid. The yellow precipitate that formed was filtered off, washed with water and dissolved in 10% isopropanol/dichloromethane (50 mL). The organic phase was dried, filtered and evaporated to dryness. The residue was chromatographed over silica gel using an ethyl acetate/petroleum ether (1:1) solvent mixture. Homogeneous fractions were pooled and evaporated, and the residue was recrystallised from dichloromethane/isopropanol to give 2-benzyloxy-4-[3-(3,5-dichloro-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-6-nitrophenol as a yellow solid (0.263 g, 49%).
3. c) To a stirred suspension of the solid obtained from above (0.24 g, 0.505 mmol) in dichloromethane (5 mL) at -78 °C under argon was added boron tribromide (0.371 g, 1.5 mmol) dropwise. The resulting purple suspension was allowed to stir at room temperature for one hour, then cooled again to -78 °C and quenched by the addition of methanol. After stirring at room temperature for one hour, the solvents were removed by evaporation. The resulting yellow foam was recrystallised

from dichloromethane/isopropanol to give the desired product as a yellow solid (0.153 g, 79%) of m.p. 252-253 °C.

Example 7

5-[3-(2-Chloro-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol (compound 8, Table 1)

[0089]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (0.50 g, 1.32 mmol) in dimethylformamide (5 mL) at room temperature was added 1,1-carbonyldiimidazole (0.246 g, 1.52 mmol) in one portion and the mixture was stirred for one hour, whereupon 2-chloro-N'-hydroxy-1-oxy-isonicotinamidine (0.284 g, 1.52 mmol) was added in one portion. The resulting mixture was stirred at room temperature for thirty minutes, then at 140 °C for four hours. After cooling to room temperature, the mixture was poured onto water (100 mL) and acidified to pH 1-2 by the dropwise addition of 2 N hydrochloric acid. The mixture was extracted with ethyl acetate and the organic extracts were washed with water and brine, then dried , filtered and evaporated to leave an orange solid that was recrystallised from dichloromethane/isopropanol to give 4-[5-(3,4-bis-benzyloxy-5-nitrophenyl)-[1,2,4]oxadiazol-3-yl]-2-chloro-pyridine 1-oxide as pale orange crystals (0.265 g, 38%).
2. b) To a stirred solution of the solid obtained above (0.25 g, 0.471 mmol) in dichloromethane (5 mL) at -78 °C under argon was added boron tribromide (0.59 g, 2.36 mmol) dropwise. The resulting deep purple suspension was allowed to stir at room temperature for one hour, then cooled again to -78 °C. The reaction was quenched by the addition of methanol, and after stirring at room temperature for one hour, the solvents were removed by evaporation. Ethanol (5 mL) and toluene (20 mL) were added to the residue and re-evaporated. The residue was triturated with boiling ethanol and filtered while warm to give the desired product as yellow crystals (0.12 g, 72%) which decomposed above 300 °C.

Example 8

2,5-Dichloro-3-(5-(3,4-dihydroxy-2-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide

[0090]

1. a) To a stirred suspension of 3-hydroxy-4-methoxy-2-nitrobenzoic acid (0.900 g, 4.22 mmol) in *N,N*-dimethylacetamide (10.35 mL) at room temperature was added 1,1-carbonyldiimidazole (1.540 g, 9.506 mmol) in 7.65 ml *N,N*-dimethylacetamide dropwise. After stirring for three hours, (Z)-2,5-dichloro-N'-hydroxy-4,6-dimethylnicotinimidamide (1.19 g, 5.107 mmol) was added in 2.7 ml of *N,N*-dimethylacetamide in one portion. The resulting mixture was stirred for one hour and forty five minutes then heated at 135 °C for one hour. The reaction mixture was poured onto ice/2N HCl mixture. The precipitate was filtered off, washed with water and dried under vacuum to give a yellow solid. Recrystallisation from dichloromethane/isopropanol gave 3-(3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)-6-methoxy-2-nitrophenol as a yellow solid (0.317 g, 18%).
2. b) To a stirred suspension of the solid obtained above (0.315 g, 0.766 mmol) in dichloromethane (4.3 mL) at room temperature was added urea hydrogen peroxide addition complex (0.231 g, 2.451 mmol). The resulting suspension was cooled to 0 °C and trifluoroacetic anhydride (0.483 g, 2.30 mmol) was added dropwise. The mixture was allowed to stir at room temperature for twenty four hours, then water was added and stirred for one hour. The precipitate was filtered off, washed with water and dried. The crude product was chromatographed in dichloromethane/methanol (99:1) mixture. Evaporation of pure fractions gave 2,5-dichloro-3-(5-(3-hydroxy-4-methoxy-2-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide as yellow crystals (0.195 g, 59%).
3. c) To a stirred suspension of the solid obtained above (0.143 g, 0.335 mmol) in N-Methylpyrrolidone (2.5 mL) at 0 °C under argon was added aluminium chloride (0.056 g, 0.42 mmol) in one portion followed by the addition of pyridine (0.106 g, 1.34 mmol). The resulting solution was heated at 60 °C for twenty-five minutes, then cooled again to room temperature and poured onto ice/2N HCl mixture. After stirring at room temperature for forty-five minutes, the precipitate was filtered off, washed with water and dried under vacuum. The crude product was recrystallized from dichloromethane/isopropanol mixture. After drying, the desired compound was obtained as yellow crystals (0.101 g, 73%) of m.p. 230 °C (dec.)

Example 9-17

[0091] By the application of the above described technique and related procedures known to those skilled in the art and using the appropriate N-hydroxy-1-oxy-isonicotinamidines, the following compounds were prepared:

3-Nitro-5-[3-(1-oxy-2-phenyl-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 264-264.8 °C (compound 9, Table 1)

5-[3-(2-Furan-3-yl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 304-305 °C (compound 10, Table 1)

5-[3-(2-Morpholin-4-yl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazo1-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 277-280 °C (compound 11, Table 1)

3-Nitro-5-[3-(1-oxy-2-thiomorpholin-4-yl-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 260-262 °C (compound 12, Table 1)

3-Nitro-5-[3-(1-oxy-2-phenylsulfanyl-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 299-301 °C (compound 13, Table 1)

3-Nitro-5-[3-(1-oxy-2-phenoxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 245-246 °C (compound 14, Table 1)

5-[3-(2,6-Dimethyl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol of, m.p. 280-282 °C (compound 15, Table 1)

5-[3-(2-Methanesulfonyl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol of, m.p. 282-285 °C (compound 16, Table 1)

5-[3-(2-Methylsulfanyl-1-oxy-pyridine-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol of, m.p. 239-240 °C (compound 17, Table 1)

Example 18

3-Nitro-5-[3-(1-oxy-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol (compound 18, Table 1)

[0092]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (0.291 g, 0.769 mmol) in dimethylformamide (5 mL) at room temperature was added 1,1-carbonyldiimidazole (0.131 g, 0.808 mmol) in one portion. After stirring for ninety minutes, N'-hydroxy-1-oxy-4-trifluoromethyl-nicotinamidine (0.17 g, 0.769 mmol) was added in one portion. The resulting mixture was stirred for two hours and then poured onto ice-water (100 mL). The precipitate was filtered off, washed with water and dried in air to give a white solid (0.192 g, 43%).
2. b) To a stirred solution of the solid obtained above (0.192 g, 0.33 mmol) in tetrahydrofuran (10 mL) at room temperature under argon, was added a 1 N solution of tetrabutylammonium fluoride in tetrahydrofuran (1.2 mL, 1.2 mmol) dropwise. After stirring at room temperature overnight, the mixture was poured onto water (100 mL) and extracted with dichloromethane. The organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed over silica gel using a dichloromethane/methanol (99:1) solvent mixture as eluent. Homogenous fractions were pooled and evaporated and the residue then recrystallised from dichloromethane/isopropanol. 3-[5-(3,4-Bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-4-trifluoromethyl-pyridine 1-oxide was obtained as a white solid (0.092 g, 49%).
3. c) To a stirred solution of the solid obtained above (0.09g, 0.16 mmol) in dichloromethane (5 mL) at -78 °C under argon was added boron tribromide (0.16 g, 0.64 mmol) dropwise. The resulting purple suspension was allowed to stir at room temperature for one hour, then cooled again to -78 °C and carefully quenched by the addition of water. After stirring at

room temperature for one hour, the precipitate was filtered off, washed with water and dried at 50 °C under vacuum to afford the desired compound as yellow crystals (0.048 g, 79%) of m.p. 239-240 °C.

Example 19-35

[0093] By the application of the above described technique and related procedures known to those skilled in the art and using the appropriate N'-hydroxy-1-oxy-isonicotinamidines, the following compounds were prepared:

5-[3-(5-Bromo-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 258-260 °C (compound 19, Table 1)

5-[3-(6-Methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 325-326 °C (compound 20, Table 1)

5-[3-(4-Methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 297 °C (compound 21, Table 1)

3-Nitro-5-[3-(1-oxy-5-phenyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 288-289 °C (compound 22, Table 1)

5-[3-(6-Chloro-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 268-270 °C (compound 23, Table 1)

5-[3-(2-Chloro-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 265-267 °C (compound 24, Table 1)

5-[3-(2-Chloro-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 218-220 °C (compound 25, Table 1)

5-[3-(2-Morpholin-4-yl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 175-177 °C (compound 26, Table 1)

5-[3-(6-Methylsulfanyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 264-266 °C (compound 27, Table 1)

3-Nitro-5-[3-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 269.5-271.3 °C (compound 28, Table 1)

5-[3-(2-Methyl-1-oxy-6-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 240-242 °C (compound 29, Table 1)

5-[3-(6-Methyl-1-oxy-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 250-252.5 °C (compound 30, Table 1)

5- [3 -(2,6-Dimethyl-1-oxy-4-trifluoromethyl-pyridin-3-yl)-[1,2,4] oxadiazol-5-yl] -3-nitro-benzene-1,2-diol, of m.p. 252-253 °C (compound 31, Table 1)

5-[3-(2-Methyl-1-oxy-6-phenyl-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 256-256.5 °C (compound 32, Table 1)

5-[3-(6-Methyl-1-oxy-2-phenyl-4-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 237-239 °C (compound 33, Table 1)

3-Nitro-5-[3-(1-oxy-quinolin-4-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 306-307 °C (compound 34, Table 1)

3-Nitro-5-[3-(1-oxy-quinolin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 276-277°C (compound 35, Table 1)

3-Nitro-5-[3-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 253-254 °C (compound 42, Table 1)

Example 36

5-[3-(2-Bromo-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol (compound 36, Table 1)

[0094]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (1.355 g, 3.576 mmol) in dimethylformamide (10 mL) at room temperature was added 1,1-carbonyldiimidazole (0.667 g, 4.113 mmol) in one portion. After stirring for ninety mintes, 2-bromo-N'-hydroxy-6-methylnicotinamidine (0.946 g, 4.113 mmol) was added and the mixture was stirred overnight then poured onto water (100 mL). Brine (10 mL) was added and the precipitate was filtered off, washed with water and dissolved in dichloromethane (50 mL). The organic layer was washed with water and brine, then dried (Na_2SO_4), filtered and evaporated to leave a white foam (1.91 g, 90%).
2. b) To a solution of the solid obtained above (1.91 g, 3.23 mmol) in dimethylformamide (30 mL) was added 1,1-carbonyldiimidazole (0.576 g, 3.55 mmol) and the resulting mixture was stirred at 120 °C for three hours, then allowed to cool to room temperature. Poured onto ice-water (150 mL) and acidified to pH 1-2 by the dropwise addition of 2 N hydrochloric acid. The mixture was extracted with dichloromethane and the organic extracts were washed with water and brine, then dried (Na_2SO_4), filtered and evaporated to leave an orange solid. Recrystallisation from dichloromethane/ethanol gave 3-[5-(3,4-bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-2-bromo-6-methyl-pyridine as an orange solid (0.702 g, 38%).
3. c) To a stirred solution of the solid obtained above (0.609 g, 1.063 mmol) in dichloromethane (15 mL) at room temperature was added urea hydrogen peroxide addition complex (0.525 g, 5.579 mmol). The resulting suspension was cooled to 0 °C and trifluoroacetic anhydride (1.12 g, 5.314 mmol) was added dropwise. The mixture was allowed to stir at room temperature for five hours, then the insoluble material was filtered off and washed with a small volume of dichloromethane. The combined filtrate was stirred with a 10% aqueous solution of sodium metabisulphite (10 mL) for fifteen minutes to destroy excess peroxides, then the phases were separated. The organic phase was washed with water, a saturated aqueous solution of sodium bicarbonate, water again and brine, then dried (Na_2SO_4), filtered and evaporated to leave a white solid. Recrystallisation twice from dichloromethane/ethanol gave 3-[5-(3,4-bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-2-bromo-6-methyl-pyridine 1-oxide as white crystals (0.344 g, 55%).
4. d) To a stirred solution of the solid obtained above (0.337 g, 0.572 mmol) in dichloromethane (10 mL) at -78 °C under argon was added boron tribromide (0.717 g, 2.86 mmol) dropwise. The resulting purple suspension was stirred at room temperature for one hour, then cooled again to -78 °C and quenched by the addition of methanol. After stirring at room temperature for one hour, the solvents were evaporated. Ethanol (5 mL) and toluene (20 mL) were added to the residue and re-evaporated. The residue was stirred in boiling ethanol and filtered while still warm. After drying, the desired compound was obtained as orange crystals (0.187 g, 80%) of m.p. 246-247 °C.

Example 37-41

[0095] By the application of the above described technique and related procedures known to those skilled in the art and using the appropriate N'-hydroxy-nicotinamidines, the following compounds were prepared:

5-[3-(2-Chloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 234-235 °C (compound 37, Table 1)

5-[3-(2-Bromo-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzene-1,2-diol, of m.p. 205-207 °C (compound 38, Table 1)

3-Nitro-5-[3-(1'-oxy-pyridin-3-ylmethyl)-[1,2,4]oxadiazol-5-yl]-benzenediol, of m.p. 232 °C (compound 39, Table 1)

3-Nitro-5-[3-(1'-oxy-6-trifluoromethyl-pyridine-3-ylmethyl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 195.2 °C (compound 43, Table 1)

3-Nitro-5-[3-(1'-oxy-5-trifluoromethyl-pyridin-2-yloxymethyl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, of m.p. 222 °C (compound 44, Table 1)

Example 42

5-[3-(2-Bromo-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol (compound 40, Table 1)

[0096]

1. a) To a stirred solution of 3,4-dibenzyloxy-5-nitrobenzoic acid (0.945 g, 2.49 mmol) in dimethylformamide (10 mL) at room temperature was added 1,1-carbonyldiimidazole (0.465 g, 2.87 mmol) in one portion, and the resulting mixture was stirred for two hours, whereupon 2-bromo-N'-hydroxy-4,5,6-trimethyl-nicotinamidine (0.74 g, 2.87 mmol) was added in one portion. The resulting mixture was allowed to stir at room temperature overnight, and then poured onto water (150 mL). Brine (10 mL) was added, and the resulting precipitate was filtered off and washed with water. The solid was then dissolved in dichloromethane (50 mL) and the organic phase was washed with water and brine, then dried, filtered and evaporated to leave an off-white solid (1.40 g, 91%).
2. b) To a stirred solution of the solid obtained above (1.39 g, 2.245 mmol) in tetrahydrofuran (20 mL) at room temperature under argon was added a 1 N solution of tetrabutylammonium fluoride in tetrahydrofuran (2.47 mL, 2.47 mmol). After stirring at room temperature overnight, the almost black reaction mixture was poured onto water (150 mL) and extracted with dichloromethane. The organic extracts were washed with water and brine, then dried, filtered and evaporated to leave a brown oil. Addition of dichloromethane (4 mL) and diethyl ether (4 mL) caused formation of a precipitate that was filtered off and recrystallised from isopropanol. 3-[5-(3,4-Bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-2-bromo-4,5,6-trimethyl-pyridine was obtained as a beige solid (0.879 g, 65%).
3. c) To a stirred solution of the pyridine obtained from above (0.621 g, 1.033 mmol) in dichloromethane (20 mL) at room temperature was added urea hydrogen peroxide complex (1.018 g, 10.82 mmol) in one portion. The resulting suspension was cooled in an ice-water bath and trifluoroacetic anhydride (2.23 g, 10.62 mmol) was added dropwise. The resulting suspension was stirred in the cold for fifteen minutes and then allowed to stir at room temperature overnight. The insoluble material was then filtered off and washed with a small volume of dichloromethane. The combined filtrate was stirred with a 10% aqueous solution of sodium metabisulphite for fifteen minutes and then the phases were separated. The organic phase was washed with water, a saturated aqueous solution of sodium bicarbonate, water again and brine, then dried , filtered and evaporated to leave a foamy pale orange solid. This solid was chromatographed over silica gel using a petroleum ether/ethyl acetate (1:1) mixture as eluent. Homogenous product containing fractions were pooled and evaporated. 3-[5-(3,4-Bis-benzyloxy-5-nitro-phenyl)-[1,2,4]oxadiazol-3-yl]-2-bromo-4,5,6-trimethyl-pyridine 1-oxide was obtained as a foamy pale yellow solid (0.342 g, 54%).
4. d) To a stirred solution of the solid obtained above (0.325 g, 0.527 mmol) in dichloromethane (10 mL) at -78 °C under argon was added boron tribromide (0.66 g, 2.633 mmol) dropwise. The resulting deep purple suspension was allowed to stir at room temperature for one hour, then cooled again to - 78 °C and carefully quenched by the dropwise addition of methanol. After stirring at room temperature for one hour, the solvents were removed by evaporation. Toluene (20 mL) and ethanol (5 mL) were added to the residue and re-evaporated. The resulting yellow solid was triturated with boiling ethanol (15 mL) and filtered whilst warm. The desired product was obtained as a yellow solid (0.172 g, 75%) of m.p. 242-243 °C.

Example 43-46

[0097] By the application of the above described technique and related procedures known to those skilled in the art and using the appropriate N'-hydroxy-nicotinamidine, the following compounds were prepared:

5-[3-(2-Chloro-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, m.p. 246-247.3 °C (compound 41, Table 1)

5-[3-(2,5-Dichloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, m.p. 237-240 °C (compound 45, Table 1)

3-Nitro-5-[3-(4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzene-1,2-diol, m.p. 255-256 °C (compound 46, Table 1)

5-[3-(2-Bromo-5-chloro-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, m.p. 227-228 °C (compound 47, Table 1)

Example 47

[0098] As an example of a compound of the general formula (I) having a 2H-pyrazol-1,5-diyl moiety as central unit, 3-nitro-5-[2-(1-oxy-2-trifluormethyl-pyridin-3-yl)-2H-pyrazol-3-yl]-benzene-1,2-diol was prepared by the following procedure:

1. a) To a stirred solution of 1-(3,4-dimethoxy-5-nitro-phenyl)-3-dimethylamino-prop-2-en-1-one (0.5 g, 1.79 mmol) and (2-trifluoromethyl-pyridin-3-yl)-hydrazine (0.33 g, 1.87 mmol) in ethanol (10 mL) was added 10 drops of concentrated hydrochloric acid and the mixture was heated at reflux for two hours. The mixture was allowed to cool to room temperature and the resulting precipitate was filtered off, washed with ethanol and dried to give 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-pyrazol-1-yl]-2-trifluoromethyl-pyridine, 0.58 g (82%).
2. b) To a solution of 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-pyrazol-1-yl]-2-trifluoromethyl-pyridine (0.50 g, 1.27 mmol) in dichloromethane (10 mL) cooled in an ice-water bath was added urea-hydrogen peroxide complex (0.26 g, 2.76 mmol) in one portion followed by trifluoroacetic anhydride (0.53 g, 2.52 mmol) dropwise. The resulting mixture was allowed to stir at room temperature overnight and then the insoluble material was filtered off. The filtrate was washed with water and brine, then dried over anhydrous sodium sulphate, filtered and evaporated to leave an off-white solid. Recrystallisation from ethanol afforded 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-pyrazol-1-yl]-2-trifluoromethyl-pyridine 1-oxide, 0.34 g (65%).
3. c) A suspension of 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-pyrazol-1-yl]-2-trifluoromethyl-pyridine 1-oxide (0.3 g, 0.73 mmol) in 48% aqueous hydrobromic acid (10 mL) was stirred at 140 °C for one hour and then allowed to cool to room temperature. The mixture was then poured onto ice-water (100 mL) and the resulting yellow precipitate was filtered off, washed with water and dried to give 3-nitro-5-[2-(1-oxy-2-trifluormethyl-pyridin-3-yl)-2H-pyrazol-3-yl]-benzene-1,2-diol, 0.16 g (57%).

Example 48

[0099] As an example of a compound of the general formula (I) having a 1,3,4-oxadiazol-2,5-diyl moiety as central unit, 3-nitro-5-[5-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-[1,3,4] oxadiazol-2-yl]-benzene-1,2-diol was prepared by the following procedure:

1. a) A mixture of 3,4-dimethoxy-5-nitrobenzoic acid (0.53 g, 2.34 mmol) and 1,1-carbonyldiimidazole (0.42 g, 2.59 mmol) was heated in tetrahydrofuran (10 mL) at reflux for three hours and then cooled to room temperature. 2-Trifluoromethyl-nicotinic acid hydrazide (0.53 g, 2.57 mmol) was added in one portion and the yellowish mixture was stirred at reflux overnight and then allowed to cool to room temperature. The mixture was poured onto cold water (100 mL) and the copious precipitate was filtered off, washed with water and dried to give 2-trifluoromethyl-nicotinic acid N'-(3,4-dimethoxy-5-nitro-benzoyl)-hydrazide, 0.71 g (73%).
2. b) A suspension of 2-trifluoromethyl-nicotinic acid N'-(3,4-dimethoxy-5-nitro-benzoyl)-hydrazide (0.60 g, 1.44 mmol) in phosphorus oxychloride (10 mL) was stirred at 130 °C for three hours, becoming a pale yellow solution. The mixture was allowed to cool to room temperature and then poured onto ice-water (200 mL). The white precipitate was filtered off, washed with water and dried to give 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-trifluoromethyl-pyridine, 0.48 g (84%).
3. c) To a stirred solution of 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-trifluoromethyl-pyridine (0.45 g, 1.13 mmol) in dichloromethane (10 mL)) cooled in an ice-water bath was added urea hydrogen peroxide complex (0.23 g, 2.45 mmol) in one portion followed by trifluoroacetic anhydride (0.47 g, 2.24 mmol) dropwise. The resulting mixture was allowed to stir at room temperature overnight and then the insoluble material was filtered off. The filtrate was washed with water and brine, then dried over anhydrous sodium sulphate, filtered and evaporated to leave an off-white solid. Recrystallisation from ethanol afforded 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-trifluoromethyl-pyridine 1-oxide, 0.39 g (83%).
4. d) A suspension of 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-trifluoromethyl-pyridine 1-oxide (0.30 g, 0.73 mmol) in a mixture of 48% hydrobromic acid (5 mL) and 30% hydrogen bromide in acetic acid (5 mL) was heated at 140 °C overnight and then allowed to cool to room temperature. After evaporation to dryness under reduced pressure, toluene (10 mL) was added to the residue and re-evaporated under reduced pressure. The resulting solid was recrystallised from isopropanol to give 3-nitro-5-[5-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-[1,3,4]oxadiazol-2-yl]-benzene-1,2-diol as a yellow solid, 0.19 g, (68%).

Example 49

[0100] As an example of a compound of the general formula (I) having a pyrimidin-2,4-diyl moiety as central unit, 3-nitro-5-[2-(1-oxy-2-trifluoromethyl-pyridine-3-yl)-pyrimidin-4-yl]-benzene-1,2-diol was prepared by the following procedure:

1. a) A stirred suspension of 1-(3,4-dimethoxy-5-nitro-phenyl)-3-dimethylamino-prop-2-en-1-one (0.28 g, 1.0 mmol), 1-oxy-2-trifluoromethyl-nicotinamidine (0.31 g, 1.5 mmol) and potassium tert-butoxide (0.17 g, 1.5 mmol) in absolute ethanol (5 mL) was heated to 80 ^{a}C in a sealed tube for one hour and then allowed to cool to room temperature. The mixture was poured onto cold water (100 mL) and the resulting precipitate was filtered off, washed with water and dried to give 4-(3,4-dimethoxy-5-nitro-phenyl)-2-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-pyrimidine, 0.31 g (73%).
2. b) A suspension of 4-(3,4-dimethoxy-5-nitro-phenyl)-2-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-pyrimidine (0.25 g, 0.59 mmol) in 48% hydrobromic acid (5 mL) was stirred at 140 °C for four hours and then allowed to cool to room temperature. The mixture was poured onto ice-water (100 mL) and the resulting filtrate was filtered off, washed with water and dried to give 3-nitro-5-[2-(1-oxy-2-trifluoromethyl-pyridine-3-yl)-pyrimidin-4-yl]-benzene-1,2-diol, 0.21 g (90%).

Example 50

[0101] As an example of a compound of the general formula (I) having a benzene-1,3-diyl moiety as central unit, 5-nitro-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-3,4-diol was prepared by the following procedure:

1. a) To a stirred solution of 4-benzyloxy-3-methoxyphenylboronic acid (1.0 g, 3.87 mmol) and 2-(3-bromo-phenyl)-6-trifluoromethyl-pyridine 1-oxide (1.12 g, 3.52 mmol) in toluene (10 mL) and ethanol (1 mL) at room temperature under argon was added 2 N aqueous sodium carbonate solution (5.41 mL, 10.82 mmol) followed by tetrakis(triphenylphosphine)palladium (0.22 g, 0.19 mmol). The resulting mixture was stirred at 90 °C for two hours and then allowed to cool to room temperature. The phases were separated and the aqueous phase was extracted with toluene (5 mL). The combined organic phases were washed with water and brine, then dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent left a brown oil that was chromatographed over silica gel (petroleum ether/ethyl acetate, 9:1) to give 2-(4'-benzyloxy-3'-methoxybiphenyl-3-yl)-6-trifluoromethyl-pyridine 1-oxide as a clear oil, 1.11 g (70%).
2. b) To a solution of 2-(4'-benzyloxy-3'-methoxybiphenyl-3-yl)-6-trifluoromethyl-pyridine 1-oxide (1.10 g, 2.44 mmol) in dichloromethane (20 mL) cooled in an ice-water bath was added a 30% solution of hydrogen bromide in acetic acid (4 mL, 20 mmol) dropwise. The resulting solution was allowed to stir at room temperature for six hours then poured onto ice-water (100 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic layers were washed with water and brine, then dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent left a brown oil that was chromatographed over silica gel (petroleum ether/ethyl acetate, 4:1) to give 3-methoxy-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-4-ol as a clear oil, 0.57 g (65%).
3. c) To a solution of 3-methoxy-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-4-ol (0.50 g, 1.38 mmol) in acetic acid (10 mL) at room temperature was added 60% nitric acid (0.12 mL, 1.52 mmol) dropwise. The resulting mixture was allowed to stir for thirty minutes then poured onto ice-water (100 mL) and the resulting precipitate was filtered off, washed with water and dried. After chromatography over silica gel (petroleum ether/ethyl acetate, 2:1), 5-methoxy-3-nitro-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-4-ol was obtained as a yellow solid, 0.34 g (60%).
4. d) To a stirred solution of 5-methoxy-3-nitro-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-4-ol (0.30 g, 0.738 mmol) in 1,2-dichloroethane (10 mL) cooled in an ice-water bath was added aluminium chloride (0.123 g, 0.922 mmol) in one portion followed by pyridine (0.233 g, 2.95 mmol) dropwise. The resulting red suspension was stirred at 80 °C for two hours, then cooled to room temperature and poured onto cold 2 N aqueous hydrochloric acid (100 mL). The precipitate was filtered off, washed with water and dried to give 5-nitro-3'-(1-oxy-6-trifluoromethyl-pyridin-2-yl)-biphenyl-3,4-diol, 0.17 g, (59%).

Example 51

[0102] As an example of a compound of the general formula (I) having a carbonyl moiety as central unit, (3,4-dihydroxy-5-nitro-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone was prepared by the following procedure:

1. a) To a solution of 4-benzyloxy-3-methoxy-bromobenzene (2.0 g, 6.82 mmol) in tetrahydrofuran (50 mL) at -78 °C under argon was added 2 N butyllithium solution in hexanes (3.75 mL, 7.5 mmol) dropwise. The resulting mixture was allowed to stir for one hour, whereupon a solution of N-methoxy-N-methyl-2-trifluoromethyl-nicotinamide (1.76 g, 7.5 mmol) in

tetrahydrofuran (20 mL) was added dropwise. The mixture was then allowed to reach room temperature over two hours, then poured onto cold 2 N aqueous hydrochloric acid (150 mL). The mixture was extracted with diethylether, and the combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent left a brown oil that was chromatographed over silica gel (petroleum ether/ethyl acetate, 2: 1) to give (4-benzyloxy-3-methoxy-phenyl)-(2-trifluoromethyl-pyridin-3-yl)-methanone, 1.72 g (65%).

2. b) To a stirred solution of (4-benzyloxy-3-methoxy-phenyl)-(2-trifluoromethyl-pyridin-3-yl)-methanone (1.60 g, 4.13 mmol) in dichloromethane (20 mL) cooled in an ice-water bath was added urea hydrogen peroxide complex (0.85 g, 9.08 mmol) in one portion followed by trifluoroacetic anhydride (1.73 g, 8.26 mmol) dropwise. The resulting mixture was then allowed to stir at room temperature overnight, whereupon insoluble material was filtered off and washed with dichloromethane (5 mL). The combined filtrate was washed with water and brine, then dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent left an orange solid that was recrystallised from ethanol to give (4-benzyloxy-3-methoxy-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone, 1.0 g (60%).
3. c) To a stirred solution of (4-benzyloxy-3-methoxy-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone (0.95 g, 2.36 mmol) in dichloromethane cooled in an ice-water bath was added dropwise a 30% solution of hydrogen bromide in acetic acid (3.54 mL, 17.7 mmol). The resulting solution was allowed to stir at room temperature overnight then poured onto ice-water (100 mL). The phases were separated and the aqueous phase extracted with dichloromethane (10 mL). The combined organic layers were washed with water and brine, then dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent left a brown oil that was chromatographed over silica gel (petroleum ether/ethyl acetate, 1:1) to give (4-hydroxy-3-methoxy-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone as a colourless solid, 0.59 g (80%).
4. d) To a solution of (4-hydroxy-3-methoxy-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone (0.50 g, 1.59 mmol) in acetic acid (10 mL) at room temperature was added 60% nitric acid (0.14 mL, 1.75 mmol) dropwise. The resulting mixture was allowed to stir for thirty minutes then poured onto ice-water (100 mL) and the resulting precipitate was filtered off, washed with water and dried. Recrystallisation from ethanol afforded (4-hydroxy-3-methoxy-5-nitro-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone as a yellow solid, 0.33 g (58%).
5. e) To a stirred solution of (4-hydroxy-3-methoxy-5-nitro-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone (0.30 g, 0.84 mmol) in 1,2-dichloroethane (10 mL) cooled in an ice-water bath was added aluminium chloride (0.14 g, 1.05 mmol) in one portion followed by pyridine (0.26 g, 3.35 mmol) dropwise. The resulting red suspension was stirred at 80 °C for two hours, then cooled to room temperature and poured onto cold 2 N aqueous hydrochloric acid (100 mL). The precipitate was filtered off, washed with water and dried to give (3,4-dihydroxy-5-nitro-phenyl)-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-methanone, 0.19 g, (66%).

Example 52

[0103] As an example of a compound of the general formula (I) having a (Z)-1-cyanoethen-1,2-diyl moiety as central unit, 3-(3,4-dihydroxy-5-nitro-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile was prepared by the following procedure:

1. a) A suspension of vanillin (1.0 g, 6.57 mmol), (1-oxy-6-trifluoromethyl-pyridin-3-yl)-acetonitrile (1.33 g, 6.57 mmol) and piperidine (0.71 mL, 7.23 mmol) in absolute ethanol (10 mL) was stirred at reflux for forty-eight hours and then allowed to cool to room temperature. The resulting precipitate was filtered off, washed with water and dried. Recrystallisation from isopropanol afforded 3-(4-hydroxy-3-methoxy-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile as white crystals, 0.95g (43%).
2. b) To a solution of 3-(4-hydroxy-3-methoxy-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile (0.90 g, 2.68 mmol) in acetic acid (20 mL) was added 60% nitric acid (0.23 mL, 2.95 mmol) dropwise. The resulting mixture was allowed to stir at room temperature for thirty minutes then poured onto ice-water (100 mL). The yellow precipitate was filtered off, washed with water and dried. Recrystallisation from isopropanol afforded 3-(4-hydroxy-3-methoxy-5-nitro-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile as a yellow solid, 0.63 g, (62%).
3. c) To a stirred solution of 3-(4-hydroxy-3-methoxy-5-nitro-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile (0.55 g, 1.44 mmol) in 1,2-dichloroethane (10 mL) cooled in an ice-water bath was added aluminium chloride (0.24 g, 1.80 mmol) in one portion followed by pyridine (0.46 g, 5.77 mmol) dropwise. The resulting red suspension was stirred at 80 °C for two hours, then cooled to room temperature and poured onto cold 2 N aqueous hydrochloric acid (100 mL). The precipitate was filtered off, washed with water and dried to give 3-(3,4-dihydroxy-5-nitro-phenyl)-2-(1-oxy-6-trifluoromethyl-pyridin-3-yl)-acrylonitrile, 0.32 g (60%).

Example 53

[0104] As an example of a compound of the general formula (I) having a 1H-imidazol-1,5-diyl moiety as central unit, 2-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-5-(trifluoromethyl)pyridine 1-oxide was prepared by the following procedure:

1. a) To a stirred solution of 2-amino-5-(trifluoromethyl)pyridine 1-oxide (0.445 g, 2.5 mmol) in a mixture of ethanol (12.5 mL) and acetic acid (0.25 mL) at room temperature was added 3,4-dimethoxy-5-nitrobenzaldehyde (0.53 g, 2.5 mmol). The reaction was heated at reflux temperature for two hours then ethanol was evaporated. The oily residue was dissolved in a mixture of methanol (17 mL) and 1,2-dimethoxyethane (7.5 mL), whereupon 1-(isocyanomethylsulfonyl)-4-methylbenzene (TOSMIC) (0.73 g, 3.75 mmol) and potassium carbonate (0.69 g, 5 mmol) were added in one portion. The resulting mixture was stirred at reflux temperature for 3 hours. The reaction was evaporated to dryness, and then taken up in dichloromethane (50 ml). The organic phase was washed with water (50 mL) and then dried over anhydrous magnesium sulphate, filtered and evaporated to leave brown oil. Column chromatography over silica gel (petroleum ether-ethyl acetate 9:1) gave 2-(5-(3,4-dimethoxy-5-nitrophenyl)-1H-imidazol-1-yl)-5-(trifluoromethyl)pyridine 1-oxide, 0.56 g (55%).
2. b) 2-(5-(3,4-Dimethoxy-5-nitrophenyl)-1H-imidazol-1-yl)-5-(trifluoromethyl)pyridine 1-oxide (0.41 g, 1 mmol) was heated at 140 °C in 48% aqueous hydrogen bromide (6 mL) for 2.5 hours. The dark homogeneous solution was cooled to room temperature and volatiles were removed by evaporation to leave a pale brown crystalline solid that was dried over P_2O_5 under vacuum. Trituration of the resulting solid with diethyl ether gave 2-(5-(3,4-dihydroxy-5-nitrophenyl)-1H-imidazol-1-yl)-5-(trifluoromethyl)pyridine 1-oxide as a yellow crystalline solid, 0.27 g (71%).

Example 54

[0105] As an example of a compound of the general formula (I) having a isoxazo-3,5-diyl moiety as central unit, 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide was prepared by the following procedure:

1. a) To a stirred suspension of (E)-3-(3-(3,4-dimethoxy-5-nitrophenyl)acryloyl)-2-(trifluoromethyl)pyridine 1-oxide (1.19 g, 3 mmol) in ethanol (15 mL) was added 50% aqueous hydroxylamine solution (0.74 mL, 4.5 mmol) and the mixture was heated to 80 °C. After stirring for 1 hour, a fine precipitate began to separate from the reaction mixture. After cooling to room temperature the yellow precipitate was filtered off, washed with ethanol and dried under vacuum to give 3-(3-(3,4-dimethoxy-5-nitrophenyl)-5-hydroxy-4;5-dihydroisoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 0.94 g (73%).
2. b) 3-(3-(3,4-dimethoxy-5-nitrophenyl)-5-hydroxy-4,5-dihydroisoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide (2.14 g, 5 mmol) was heated in 20 mL of ethyl acetate to 70 °C. To the resulting slurry was added trifluoroacetic acid (0.74 g, 6.5 mmol) dropwise. After 10 minutes, the reaction was evaporated to dryness and the residue was recrystallised from isopropanol to give 3-(3-(3,4-dimethoxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide, 1.27 g (62%).
3. c) 3-(3-(3,4-dimethoxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl) pyridine 1-oxide (0.81 g, 2 mmol) was taken up in dichloromethane (15 mL) and the yellowish suspension was cooled to -78 °C under argon whereupon boron tribromide (4.5 g, 18 mmol) was added dropwise. The reddish reaction mixture was allowed to warm to room temperature and stirred for 18 hours, then carefully poured into ice-water (100 mL) and allowed to stir for 1 hour. The yellow precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. Trituration with boiling ethanol gave 3-(3-(3,4-dihydroxy-5-nitrophenyl)isoxazol-5-yl)-2-(trifluoromethyl)pyridine 1-oxide as a yellow solid, 0.49 g (64%).

Example 55

[0106] As an example of a compound of the general formula (I) having a furan-2,4-diyl moiety as central unit, 3-(4-(3,4-dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-(trifluoromethyl)pyridine-1-oxide was prepared by the following procedure:

1. a) To a stirred solution of 3-(3-ethoxy-3-oxopropanoyl)-2-(trifluoromethyl)pyridine-1-oxide (1.39 g, 5 mmol) in pyridine (25 mL) was added 2-bromo-1-(3,4-dimethoxy-5-nitrophenyl)ethanone (1.67 g, 5.5 mmol). The reaction mixture was heated to 70 °C and stirred for 5 hours, then cooled to room temperature and poured onto 6 N aqueous HCl (100 mL). The precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. The solid was recrystallised from

dichloromethane/ispropanol to give crude 3-(4-(3,4-dimethoxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 1.05 g (43%).

2. b) 3-(4-(3,4-Dimethoxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-(trifluoro-methyl)pyridine-1-oxide (482 mg, 1 mmol) was taken up in dichloromethane (8 mL). The yellowish suspension was cooled to -78 °C under argon and boron tribromide (0.85 mL, 9 mmol) was added dropwise. The reddish reaction mixture was allowed to warm to room temperature and stirred for 18 hours and then carefully poured into ice-water (100 mL) and stirred for 1 hour. The yellow precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. Recrystallisation of the solid from ethanol gave 3-(4-(3,4-Dihydroxy-5-nitrophenyl)-3-(ethoxycarbonyl)furan-2-yl)-2-(trifluoromethyl)pyridine 1-oxide as a yellow solid, 0.31 g (68%).

Example 56

[0107] As an example of a compound of the general formula (I) having a oxazol-2,4-diyl moiety as central unit, 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide was prepared by the following procedure:

1. a) To a solution of 2-(3,4-dimethoxy-5-nitrophenyl)-2-oxoethyl acetate (4.24 g, 15 mmol) in xylene (30 mL) were added 3-carbamoyl-2-(trifluoromethyl)pyridine 1-oxide (3.40 g, 16.5 mmol) and boron trifluoride etherate (0.18 mL, 15 mmol). The resulting yellow solution was heated to reflux for 18 hours and then cooled to room temperature. After evaporation of the solvent, the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with brine and the dried over anhydrous magnesium sulphate, filtered and evaporated. The pure 3-(4-(3,4-dimethoxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl) pyridine 1-oxide was obtained by column chromatography over silica gel (petroleum ether/ethylacetate 2:1) as a pale yellow solid, 2.58 g (42%).
2. b) 3-(4-(3,4-Dimethoxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide (1.23 g, 3 mmol) was taken up in dichloromethane (25 mL). The yellowish suspension was cooled to -78 °C under argon and boron tribromide (2.55 mL, 27 mmol) was added dropwise. The red reaction mixture was allowed to warm to room temperature and stirred for 18 hours. It was then carefully poured into ice-water (100 mL) and stirred for 1 hour. The resulting yellow precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. The solid was recrystallized from ethanol to give 3-(4-(3,4-dihydroxy-5-nitrophenyl)oxazol-2-yl)-2-(trifluoromethyl)pyridine 1-oxide as a yellow solid, 0.65 g, (57%).

Example 57

[0108] As an example of a compound of the general formula (I) having a 1,2,4-triazin-3,5-diyl moiety as central unit, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide was prepared by the following procedure:

1. a) To a stirred solution of (Z)-3-carbamohydrazonoyl-2-(trifluoromethyl) pyridine 1-oxide (1.10 g, 5 mmol) in ethanol (30 mL) was added 2-(3,4-dimethoxy-5-nitrophenyl)-2-oxoacetaldehyde (1.19 g, 5 mmol). The reaction mixture was heated to reflux for 5 hours, and then cooled to room temperature and the solvent was removed by evaporation. The residue was dissolved in dichloromethane (30 mL) and the organic phase was washed with water and dried over anhydrous magnesium sulphate, filtered and evaporated. The crude product was recrystallized from isopropanol to give 3-(5-(3.4-dimethoxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide, 1.69 g (80%).
2. b) 3-(5-(3,4-dimethoxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide (1.27 g, 3 mmol) was taken up in dichloromethane (25 mL). The yellowish solution was cooled to -78 °C under argon and boron tribromide (2.55 mL, 27 mmol) was added dropwise. The red reaction mixture was allowed to warm to room temperature and stirred for 18 hours. It was then carefully poured into ice-water (100 mL) and stirred for 1 hour. The yellow precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. The solid was recrystallised from dichloromethane-ethanol to give 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-triazin-3-yl)-2-(trifluoromethyl)pyridine 1-oxide as a yellow solid, 0.84 g (71%).

Example 58

[0109] As an example of a compound of the general formula (I) having a 1,3,5-triazin-2,4-diyl moiety as central unit, 3-(4-(3,4-

dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide was prepared by the following procedure:

1. a) To a solution of (*E*)-N-((dimethylamino)methylene)-3,4-dimethoxy-5-nitrobenzamide (1.12 g, 4 mmol) ethanol (30 mL) was added 3-carbamimidoyl-2-(trifluoromethyl)pyridine 1-oxide (0.82 g, 4 mmol). The reaction mixture was heated to reflux for 5 hours. It was cooled to room temperature and the solvent was removed by evaporation. The residue was then dissolved in dichloromethane/isopropanol mixture (50 mL, 70:30) and the organic phase was washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated. The crude product was recrystallized from ethanol to give 3-(4-(3,4-dimethoxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide, 1.27 g (75%).
2. b) A portion of 3-(4-(3,4-dimethoxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl) pyridine 1-oxide (1.269 g, 3 mmol) was taken up in dichloromethane (25 mL). The yellowish solution was cooled to -78 °C under argon and boron tribromide (2.55 mL, 27 mmol) was added dropwise. The red reaction mixture was allowed to warm to room temperature and stirred for 18 hours and then carefully poured into ice-water (100 mL) and stirred for 1 hour. The yellow precipitate was filtered off, washed with water and dried over P_2O_5 under vacuum. Recrystallisation from a dichloromethane-ethanol mixture gave 3-(4-(3,4-dihydroxy-5-nitrophenyl)-1,3,5-triazin-2-yl)-2-(trifluoromethyl)pyridine 1-oxide as a yellow solid, 1.07 g (90%).

Example 59

[0110] As an example of a compound of the general formula (I) having a pyrrol-2,5-diyl moiety as central unit, 5-(3,4-dihydroxy-5-nitrophenyl)-1-methyl-2-(2-trifluoromethyl-1-oxypyridin-3-yl)-1H-pyrrole-3-carboxylic acid ethyl ester was prepared by the following procedure:

1. a) To a stirred solution of methylamine (0.63 mL, 33% EtOH solution, 5 mmol) in a mixture of ethanol (25 mL) and acetic acid (0.5 mL) at room temperature was added 3-oxo-3-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-propionic acid ethyl ester (1.39 g, 5 mmol). The reaction mixture was heated at reflux for two hours whereupon the solvent was removed by evaporation under vacuum. To a solution of the crude product in dimethylformamide (25 mL) was added potassium carbonate (2.07 g, 15 mmol) in one portion followed by 1-(3,4-bis-benzyloxy-5-nitro-phenyl)-2-bromo-ethanone (2.51 g, 5.50 mmol) and the mixture was then stirred at 100 °C. Once no starting material was detectable by TLC, the reaction mixture was allowed to cool to room temperature and poured onto ice-cold 1 N aqueous hydrochloric acid (100 mL). The resulting precipitate was filtered off, washed with water and dried. The residue was chromatographed over silica gel. Homogeneous fractions were pooled and evaporated to give 5-(3,4-bis-benzyloxy-5-nitro-phenyl)-1-methyl-2-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-1H-pyrrole-3-carboxylic acid ethyl ester, 2.41 g (79%).
2. b) A solution of 5-(3,4-bis-benzyloxy-5-nitro-phenyl)-1-methyl-2-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-1H-pyrrole-3-carboxylic acid ethyl ester (0.2 g, 0.30 mmol) in dichloromethane (10 mL) was cooled to -78 °C with stirring and treated under argon with boron tribromide (0.30 g, 1.21 mmol). The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -78 °C. The mixture was quenched by the careful addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give 5-(3,4-dihydroxy-5-nitro-phenyl)-1-methyl-2-(1-oxy-2-trifluoromethyl-pyridin-3-yl)-1H-pyrrole-3-carboxylic acid ethyl ester as a yellow solid, 0.13 g (93%).

Example 60

[0111] As an example of a compound of the general formula (I) having a 2H-tetrazol-2,5-diyl moiety as central unit, 5-[2-(5-trifluoromethyl-1-oxy-pyridin-2-yl)-2H-tetrazol-5-yl]-3-nitrobenzene-1,2-diol was prepared by the following procedure:

1. a) A mixture of 3,4-bis-benzyloxy-5-nitro-benzonitrile (0.54 g, 1.50 mmol), sodium azide (0.15 g, 2.25 mmol) and ammonium chloride (0.12 g, 2.25 mmol) in dimethylformamide (3 mL) was stirred at 85 °C for 20 hours. After cooling to room temperature, the reaction mixture was poured onto water (30 mL) and acidified with dilute hydrochloric acid. The resulting precipitate was collected, washed with water and dried to yield 5-(3,4-bis-benzyloxy-5-nitro-phenyl)-2H-tetrazole, 0.53 g (87%).
2. b) 2-Chloro-5-trifluoromethyl-1-oxy-pyridine (0.20 g, 1.00 mmol) was added to a stirred suspension of 5-(3,4-bis-benzyloxy-5-nitro-phenyl)-2H-tetrazole (0.4 g, 1.00 mmol) and potassium carbonate (0.14 g, 1 mmol) in acetonitrile (10 mL). The

reaction mixture was stirred at room temperature till completion, then diluted with dichloromethane and washed with water. The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to leave a crude residue that was recrystallised from a dichloromethane/isopropanol mixture to afford 2-[5-(3,4-bis-benzyloxy-5-nitro-phenyl)-tetrazol-2-yl]-5-trifluoromethyl-1-oxy-pyridine, 0.40 g (71%).

3. c) A solution of 2-[5-(3,4-bis-benzyloxy-5-nitro-phenyl)-tetrazol-2-yl]-5-trifluoromethyl-1-oxy-pyridine (0.282 g, 0.5 mmol) in dichloromethane (15 mL) was cooled to -78 °C with stirring under argon and treated with boron tribromide (1.00 g, 4.00 mmol) dropwise. The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -78 °C. The mixture was quenched by the careful addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give 5-[2-(5-trifluoromethyl-1-oxy-pyridin-2-yl)-2H-tetrazol-5-yl]-3-nitrobenzene-1,2-diol as a yellow solid, 0.17 g, (90%).

Example 61

[0112] As an example of a compound of the general formula (I) having a 1,3-thiazol-2,4-diyl moiety as central unit, 5-[2-[2-(trifluoromethyl)-1-oxy-pyridin-3-yl]-[1,3]-thiazol-4-yl]-3-nitrobenzene-1,2-diol was prepared by the following procedure:

1. a) A mixture of 2-(trifluoromethyl)-1-oxy-pyridine-3-carbothioamide (0.24 g, 1.10 mmol) and 1-[3,4-bis(benzyloxy)-5-nitrophenyl]-2-bromoethanone (0.50 g, 1.10 mmol) were refluxed overnight in absolute ethanol (5 mL). After cooling to room temperature, the reaction mixture was poured onto water (50 mL). The resulting precipitate was filtered off, washed with water (25 mL) and dried. Recrystallisation from dichloromethane/isopropanol afforded 3-[4-(3,4-bis-benzyloxy-5-nitro-phenyl) -[1,3]-thiazol-2-yl]-2-trifluoromethyl-1-oxy-pyridine, 0.55 g (87%).
2. b) A solution of 3-[4-(3,4-bis-benzyloxy-5-nitro-phenyl)-[1,3]-thiazol-2-yl]-2-trifluoromethyl-1-oxy-pyridine (0.15 g, 0.26 mmol), in dichloromethane (10 mL) was cooled to -78 °C and treated under argon, with boron tribromide (0.26 g, 1.03 mmol). The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -78 °C. The mixture was quenched by careful addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give 5-[2-[2-(trifluoromethyl)-1-oxy-pyridin-3-yl]-[1,3]-thiazol-4-yl]-3-nitrobenzene-1,2-diol as a yellow solid, 0.09 g (87%).

Example 62

[0113] As an example of a compound of the general formula (I) having a 1,2,4-triazol-3,5-diyl moiety as central unit, 5-[4-methyl-5-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-3-nitro-benzene-1,2-diol was prepared by the following procedure:

1. a) To a stirred solution of 3,4-dimethoxy-5-nitro-benzoyl chloride (0.50 g, 2.04 mmol) in dichloromethane (10 mL) at 0 °C, was added dropwise methylamine (1.02 mL, 2.04 mmol, 2 M in THF). The reaction mixture was stirred at room temperature till all starting material disappeared, then diluted with dichloromethane and washed with water. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to leave a crude residue that was recrystallised from a dichloromethane/isopropanol mixture to afford 3,4-dimethoxy-N-methyl-5-nitrobenzamide, 0.44 g (89%).
2. b) To a stirred suspension of 3,4-dimethoxy-N-methyl-5-nitro-benzamide (0.40 g, 1.66 mmol) in toluene (10 mL) was added phosphorous pentachloride (0.38 g, 1.83 mmol) portionwise. Upon completion of addition, the reaction mixture was warmed to reflux till complete disappearance of starting material. Evaporation to dryness resulted in a crude solid that was washed with diethyl ether, affording 3,4-dimethoxy-N-methyl-5-nitro-benzimidoyl chloride, 0.37 g (85%).
3. c) A mixture of 2-trifluoromethyl-1-oxy-3-pyridinecarbonitrile (0.47 g, 2.50 mmol), sodium azide (0.24 g, 3.75 mmol) and ammonium chloride (0.20 g, 3.75 mmol) in dimethylformamide (2.5 mL) was stirred at 85 °C for 20 hours. After cooling to room temperature, the reaction mixture was poured onto water (20 mL) and acidified with dilute hydrochloric acid. The resulting precipitate was collected, washed with water and dried to yield 3-(2H-tetrazol-5-yl)-2-trifluoromethyl-1-oxy-pyridine, 0.52 g (90%).
4. d) 3,4-Dimethoxy-N-methyl-5-nitro-benzimidoyl chloride (0.26 g, 1.08 mmol) was added to a stirred solution of 3-(2H-tetrazol-5-yl)-2-trifluoromethyl-1-oxy-pyridine (0.23 g, 1 mmol) in dry pyridine (3 mL), preheated to 50 °C. The resulting mixture was cautiously heated to 75-90 °C and maintained at this temperature until nitrogen evolution ceased. The mixture

was then poured onto water (30 mL) and extracted with dichloromethane (25 mL). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The resulting residue was purified by chromatography to afford 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-2-trifluoromethyl-1-oxy-pyridine, 0.25 g (59%).

5. e) To a stirred suspension of 3-[5-(3,4-dimethoxy-5-nitro-phenyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-2-trifluoromethyl-1-oxy-pyridine (0.20 g, 0.47 mmol) in dichloromethane (20 mL) at -78 °C under argon was added boron tribromide (0.47 g, 1.88 mmol) dropwise. The resulting purple suspension was then allowed to stir at room temperature for seven hours before being cooled in an ice-water bath. The mixture was carefully quenched by the addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give, after drying, 5-[4-Methyl-5-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-3-nitro-benzene-1,2-diol was obtained as an orange solid, 0.16 g (86%).

Example 63

[0114] As an example of a compound of the general formula (I) having a 1,2,3-thiadiazol-4,5-diyl moiety as central unit, 5-[5-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-[1,2,3]thiadiazol-4-yl]-3-nitrobenzene-1,2-diol was prepared by the following procedure:

1. a) A mixture of 1-(3,4-bis-benzyloxy-5-nitro-phenyl)-2-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-ethanone (0.50 g, 0.93 mmol), ethyl carbazate (0.11 g, 1.06 mmol) and p-toluenesulfonic acid (4 mg) in toluene (10 mL) was refluxed until azeotropic distillation of water ceased. The reaction mixture was cooled to room temperature, the solvents were evaporated to dryness, and the crude solid was triturated with diethyl ether (15 mL), filtered and dried yielding N'-[1-(3,4-bis-benzyloxy-5-nitro-phenyl)-2-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester, 0.49 g (84%).
2. b) A mixture of N'-[1-(3,4-bis-benzyloxy-5-nitro-phenyl)-2-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (0.40 g, 0.64 mmol), in thionyl chloride (2 mL) was refluxed until no more starting material was detected by TLC. Excess of solvent was removed and the residue was purified by chromatography over silica gel using a mixture of dichloromethane/ethanol as eluent. Homogeneous fractions were pooled and evaporated to afford 3-[4-(3,4-bis-benzyloxy-5-nitro-phenyl)-[1,2,3]thiadiazol-5-yl]-2-trifluoromethyl-1-oxy-pyridine, 0.19 g (51%).
3. c) A solution of 3-[4-(3,4-bis-benzyloxy-5-nitro-phenyl)-[1,2,3]thiadiazol-5-yl]-2-trifluoromethyl-1-oxy-pyridine (0.15 g, 0.26 mmol) in dichloromethane (10 mL) was cooled to -78 °C with stirring and treated under argon with boron tribromide (0.26 g, 1.03 mmol). The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -40 °C. The mixture was quenched by the careful addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give 5-[5-(2-trifluoromethyl-1-oxy-pyridin-3-yl)-[1,2,3]thiadiazol-4-yl]-3-nitrobenzene-1,2-diol as a yellow solid, 0.09 g (89%).

Example 64

[0115] As an example of a compound of the general formula (I) having a 1,2,4-oxadiazol-3,5-diyl moiety as central unit, 5-[5-[2-(trifluoromethyl)-1-oxypyridin-3-yl]-[1,2,4]-oxadiazol-3-yl]-3-nitrobenzene-1,2-diol was prepared by the following procedure:

1. a) To a stirred solution of 2-trifluoromethyl nicotinic acid (0.38 g, 2 mmol) in dimethylformamide (10 mL) at room temperature was added 1,1-carbonyldiimidazole (0.34 g, 2.10 mmol) in one portion. The resulting yellow mixture was allowed to stir for ninety minutes whereupon 3,4-bis(benzyloxy)-N'-hydroxy-5-nitrobenzamidine (0.79 g, 2 mmol) was added in one portion. The resulting mixture was stirred at room temperature for two hours and then poured onto water (100 mL). The resulting precipitate was filtered off, washed with water and dried. After recrystallisation from dichloromethane/isopropanol 3,4-bis(benzyloxy)-5-nitro-N'-(2-(trifluoromethyl)nicotinoyloxy)benzimidamide was obtained, as a light yellow solid, 0.88 g (78%).
2. b) To a stirred solution of the solid obtained above (0.26 g, 0.46 mmol) in tetrahydrofuran (15 mL) at room temperature under argon was added a 1 N solution of tetrabutylammonium fluoride in tetrahydrofuran (0.7 mL, 0.7 mmol). The resulting clear yellow solution was allowed to stir at room temperature for four hours. Additional tetrabutylammonium fluoride (0.7 mmol) was added and the reaction mixture was allowed to stir for fifteen hours at room temperature and then ten hours at

55 °C. After cooling to room temperature, the reaction mixture was poured onto water (150 mL). The resulting precipitate was filtered off, washed with water and dried. The crude product was chromatographed over silica gel using dichloromethane as eluent. Homogeneous fractions were pooled and evaporated to afford 3-[3-[3,4-bis(benzyloxy)-5-nitrophenyl]-[1,2,4]-oxadiazol-5-yl]-2-(trifluoromethyl)pyridine as an off-white solid, 0.21 g (82%).

3. c) To a stirred solution of 3-[3-[3,4-bis(benzyloxy)-5-nitrophenyl]-[1,2,4]-oxadiazol-5-yl]-2-(trifluoromethyl)pyridine (0.33 g, 0.60 mmol) in dichloromethane (6 mL) at 0 °C was added urea hydrogen peroxide complex (0.28 g, 3 mmol) and trifluoroacetic anhydride (0.43 mL, 3.00 mmol). After the reaction mixture had been stirred at room temperature for 60 hours, solid residues were filtered off. The organic phase was then successively treated with an aqueous solution of $Na_2S_2O_5$ (0.6 g, 3.45 mmol, dissolved in 20 mL of water), 0.4 N hydrochloric acid (20 mL), a saturated solution of $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed over silica gel using dichloromethane/ethanol as eluent. Homogeneous fractions were pooled and evaporated, and the residue was recrystallised from dichloromethane/isopropanol to afford 3-[3-[3,4-bis(benzyloxy)-5-nitrophenyl]-[1,2,4]-oxadiazol-5-yl]-2-(trifluoromethyl)-1-oxy-pyridine as a yellow solid, 0.23 g (68%).
4. d) A solution of 3-[3-[3,4-bis(benzyloxy)-5-nitrophenyl]-[1,2,4]-oxadiazol-5-yl]-2-(trifluoromethyl)-1-oxy-pyridine (0.10 g, 0.18 mmol) in dichloromethane (5 mL) was cooled to -78 °C with stirring under argon and treated with boron tribromide (0.18 g, 0.74 mmol) dropwise. The resulting deep purple suspension was then allowed to stir at room temperature for one hour before cooling again to -78 °C. The mixture was quenched by the careful addition of methanol. After stirring at room temperature for thirty minutes, the volatiles were evaporated and the residue stirred with 2 N hydrochloric acid (5 mL) for thirty minutes. The resulting solid was filtered off, washed with water (25 mL) and then cold isopropanol (5 mL) to give 5-[5-[2-(trifluoromethyl)-1-oxypyridin-3-yl]-[1,2,4]-oxadiazol-3-yl]-3-nitrobenzene-1,2-diol as a yellow solid, 0.06 g (88%).

REFERENCES CITED IN THE DESCRIPTION

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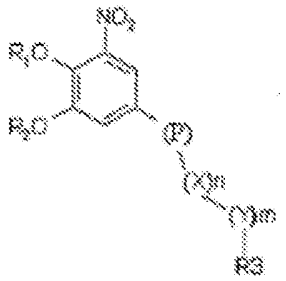
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NITROCATECHOLDERIVATER SOM COMT-INHIBITORER

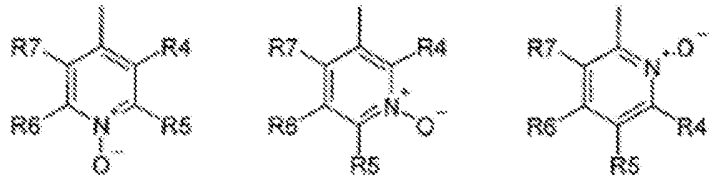
PATENTKRAV

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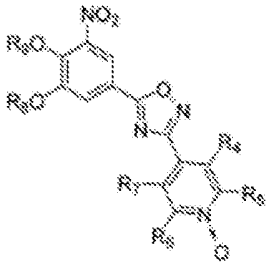
hvor R_1 og R_2 uafhængigt af hinanden er hydrogen; X repræsenterer en methylengruppe; Y repræsenterer et oxygen- eller svovlatom; n repræsenterer tallet 0, 1, 2 eller 3 og m repræsenterer tallet 0 eller 1; R_3 repræsenterer en pyridin N-oxid-gruppe med formlen A, B eller C, der er forbundet som angivet med den ikke-markerede binding:



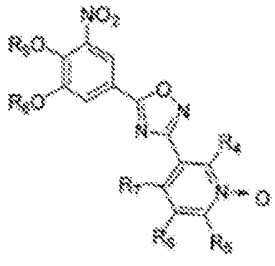
A B C

hvor R_4, R_5, R_6 og R_7 uafhængigt af hinanden repræsenterer C_1-C_6-alkyl, C_1-C_6-thioalkyl, C_1-C_6-alkoxy, C_6-C_{12}-aryloxy eller en C_6-C_{12}-thioaryl-gruppe, C_1-C_6-alkanoyl- eller C_7-C_{13}-aroyl-gruppe, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_3-C_{12}-cycloalkylamino eller C_3-C_{12}-heterocycloalkylamino, C_1-C_6-alkylsulfonyl eller C_6-C_{12}-arylsulfonyl, halogen, C_1-C_6-haloalkyl, trifluormethyl, cyano, nitro eller en heteroaryl-gruppe; eller hvor to eller flere af resterne R_4, R_5, R_6 og R_7 tilsammen repræsenterer alifatiske eller heteroalifatiske ringe eller aromatiske eller heteroaromatiske ringe, og hvor P repræsenterer en central enhed, der er udvalgt blandt regioisomerer af 1,2,4-oxadiazol-3,5-diyl og 1,3,4-oxadiazol-2,5-diyl, og hvor regioisomererne af den centrale enhed indbefatter både regioisomerer, der kan realiseres ved udskiftning af nitrocatecholdelen og $-(X)_n-(Y)_m-R_3$-delen.

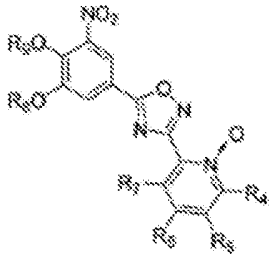
2. Forbindelse ifølge krav 1 med formlen IVA, IVB eller IVC,



IVA



IVB



IVC,

hvor R_4, R_5, R_6 og R_7 er defineret som i krav 1, hvor R_8 og R_9 repræsenterer hydrogen, eller et farmaceutisk acceptabelt salt deraf.

3. Forbindelse ifølge krav 1, der er udvalgt fra 5-[3-(3,5-dichlor-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-chlor-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-morfolin-4-yl-1-oxy-pyridin-4-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 3-nitro-5-[3-(1-oxy-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzen-1,2-diol, 5-[3-(4-brom-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-chlor-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-morfolin-4-yl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 3-nitro-5-[3-(1-oxy-6-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl)-benzen-1,2-diol, 5-[3-(2-methyl-1-oxy-6-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(6-methyl-1-oxy-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2,6-dimethyl-1-oxy-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-methyl-1-oxy-6-phenyl-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(6-methyl-1-oxy-2-phenyl-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-brom-6-methyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-chlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-brom-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol, 5-[3-(2-brom-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol, 5-[3-(2-chlor-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol, 5-[3-(2,5-dichlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol, 5-[3-(2-brom-5-chlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-

nitrobenzen-1,2-diol og 3-nitro-5-[3-(1-oxy-2-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzen-1,2-diol.

4. Forbindelse ifølge krav 1, der er 3-nitro-5-[3-(1-oxy-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzen-1,2-diol.

5. Forbindelse ifølge krav 1, der er 5-[3-(2-methyl-1-oxy-6-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol.

6. Forbindelse ifølge krav 1, der er 5-[3-(6-methyl-1-oxy-4-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitro-benzen-1,2-diol.

7. Forbindelse ifølge krav 1, der er 5-[3-(2-chlor-4,5,6-trimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol.

8. Forbindelse ifølge krav 1, der er 3-nitro-5-[3-(1-oxy-2-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzen-1,2-diol.

9. Forbindelse ifølge krav 1, der er 3-nitro-5-[3-(1-oxy-6-trifluormethyl-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-benzen-1,2-diol.

10. Forbindelse ifølge krav 1, der er 5-[3-(2,5-dichlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol.

11. Forbindelse ifølge krav 1, der er 5-[3-(2-brom-5-chlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol.

12. Farmaceutisk sammensætning omfattende en forbindelse ifølge et hvilket som helst af kravene 1 til 11 i kombination med et farmaceutisk acceptabelt bærestof.

13. Farmaceutisk sammensætning ifølge krav 12, hvor det farmaceutisk acceptable bærestof er et faststof, hvor det faste præparat er i form af pulver og/eller tabletter og/eller dispergible granulater og/eller kapsler.

14. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 til anvendelse i terapi.

15. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af et individ, der er ramt af lidelser i centralnervesystemet eller det perifere nervesystem.

16. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af humørsvingninger, Parkinsons sygdom og Parkinson-lidelser, restless leg-syndrom, gastointestinale lidelser, tilstande med ødemdannelse eller hypertension.

17. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 til anvendelse som en COMT-inhibitor.

18. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af Parkinsons sygdom.

19. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af Parkinson-lidelser.

20. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af restless leg-syndrom.

21. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller sammensætning ifølge krav 12 eller 13 til anvendelse i behandlingen af tilstande med ødemdannelse eller hypertension.

22. Forbindelse eller sammensætning til anvendelse ifølge krav 18 eller 19, hos en patient, der behandles med L-DOPA og en perifer AADC-inhibitor.

23. Forbindelse ifølge krav 1, hvor forbindelsen er 5-[3-(2,5-dichlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol til anvendelse i behandlingen af Parkinsons sygdom hos en patient, der behandles med L-DOPA og en perifer AADC-inhibitor.

24. Farmaceutisk sammensætning ifølge krav 12, hvor forbindelsen er 5-[3-(2,5-dichlor-4,6-dimethyl-1-oxy-pyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzen-1,2-diol til anvendelse i behandlingen af Parkinsons sygdom hos en patient, der behandles med L-DOPA og en perifer AADC-inhibitor.